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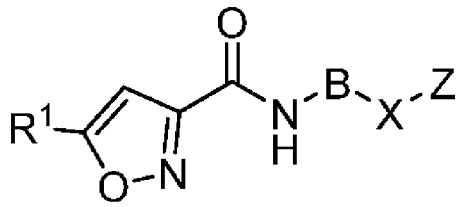
(54) **Title**: SUBSTITUTED PIPERIDINE COMPOUNDS



(I)

(57) **Abstract**: The present disclosure provides substituted piperidine compounds having Formula (I), and the pharmaceutically acceptable salts and solvates thereof, wherein R^1, B, X, and Z are defined as set forth in the specification. The present disclosure is also directed to the use of compounds of Formula I to treat a disorder responsive to the blockade of SMYD proteins such as SMYD3 or SMYD2. Compounds of the present disclosure are especially useful for treating cancer.

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SUBSTITUTED PIPERIDINE COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides substituted piperidines as SMYD protein inhibitors, such as SMYD3 and SMYD2 inhibitors, and therapeutic methods of treating conditions and diseases wherein inhibition of SMYD proteins such as SMYD3 and SMYD2 provides a benefit.

Background

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases. Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, SMYD proteins such as SMYD3 and SMYD2), many of which are associated with genetic alterations that can cause human disease, such as proliferative disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of SMYD proteins such as SMYD3 and SMYD2.

BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, the present disclosure provides substituted piperidine compounds represented by any one of Formulae **I-X** below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Disclosure."

[0004] In another aspect, the present disclosure provides a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

[0005] In another aspect, the present disclosure provides a method of inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a mammal, comprising

administering to the mammal an effective amount of at least one Compound of the Disclosure.

[0006] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition, *e.g.,* cancer, responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, comprising administering a therapeutically effective amount of a Compound of the Disclosure.

[0007] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD3.

[0008] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD2.

[0009] In another aspect, the present disclosure provides the use of Compounds of the Dicslosure as inhibitors of SMYD proteins.

[0010] In another aspect, the present disclosure provides a pharmaceutical composition for treating a disease, disorder, or condition responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, wherein the pharmaceutical composition comprises a therapeutically effective amount of a Compound of the Disclosure in a mixture with one or more pharmaceutically acceptable carriers.

[0011] In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating cancer in a mammal, *e.g.*, breast, cervical, colon, kidney, liver, head and neck, skin, pancreatic, ovary, esophageal, lung, and prostate cancer.

[0012] In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating cancer in a mammal.

[0013] In another aspect, the present disclosure provides kit comprising a Compound of the Disclosure.

[0014] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0015] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

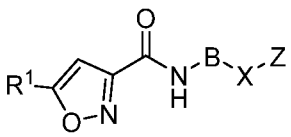
DETAILED DESCRIPTION OF THE INVENTION

[0016] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD proteins. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.,* cancer, responsive to inhibition of SMYD proteins.

[0017] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD3. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.,* cancer, responsive to inhibition of SMYD3.

[0018] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD2. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.,* cancer, responsive to inhibition of SMYD2.

[0019] In one embodiment, Compounds of the Disclosure are compounds having Formula **I**:

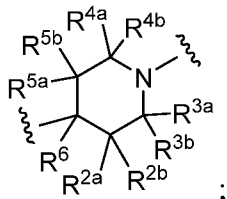


I

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof,

wherein:

[0020] B is:



;

[0021] X is selected from the group consisting of $-S(=O)_2-$, $-S(=O)_2N(R^7)-$, $-S(=O)_2C(R^8)(H)-$, $-C(=O)-$, $-C(=O)N(R^7)-$, $-C(=O)O-$, $-C(=O)C(R^8)(H)-$, and $-S(=O)_2N(R^7)C(=O)N(R^{11})-$; or X is absent, (*i.e.*, Z forms a bond with the nitrogen atom),

[0022] wherein the sulfur atom of $-S(=O)_2N(R^7)-$, $-S(=O)_2C(R^8)(H)-$, or $-S(=O)_2N(R^7)C(=O)N(R^{11})-$ is attached to the nitrogen atom of B, the carbon atom of $-C(=O)N(R^7)-$ or $-C(=O)O-$ is attached to the nitrogen atom of B, and the carbonyl carbon atom of $-C(=O)C(R^8)(H)-$ is attached the nitrogen atom of B;

[0023] Z is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, fluoroalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, [(cycloalkyl)alkylamino]alkyl, [(heterocyclo)alkylamino]alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and heteroaralkyl;

[0024] R^1 is selected from the group consisting of ethyl, n-propyl, isopropyl, isobutyl, and cyclopropyl;

[0025] R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or

[0026] R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0027] R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0028] R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0029] R^{5a} and R^{5b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0030] R^{2a} and R^{5a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0031] R^{3a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0032] R^{2a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0033] R^{3a} and R^{5a} taken form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

[0034] R^6 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

[0035] R^7 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

[0036] R^8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and $-N(R^9)C(=O)R^{10}$;

[0037] R^9 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

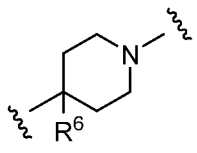
[0038] R^{10} is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, and (dialkylamino)alkyl; and

[0039] R^{11} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

[0040] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is selected from the group consisting of ethyl and cyclopropyl.

[0041] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is selected from the group consisting of optionally substituted C_{1-6} alkyl, fluoroalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and heteroaralkyl, when X is absent.

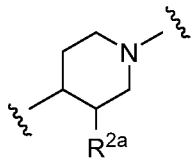
[0042] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



;

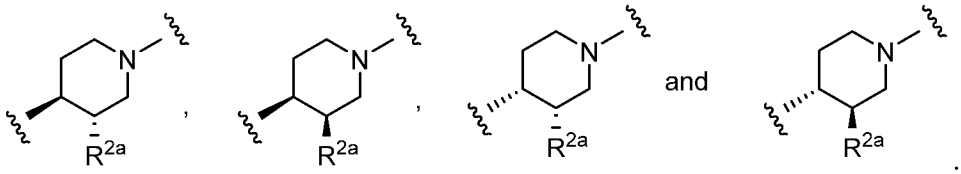
R^6 is selected from the group consisting of hydrogen and C_{1-4} alkyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, R^6 is selected from the group consisting of hydrogen and methyl. In another embodiment, R^6 is hydrogen.

[0043] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



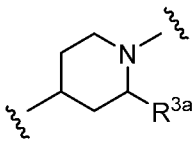
;

R^{2a} is selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



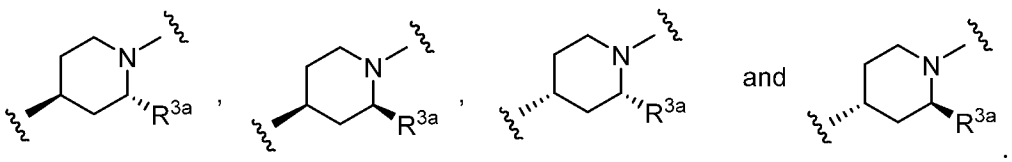
In another embodiment, R^{2a} is selected from the group consisting of methyl, ethyl, phenyl, $-CF_3$, $-CO_2Et$, and $-CH_2OH$. In another embodiment, R^{2a} is $-CH_2Ph$.

[0044] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



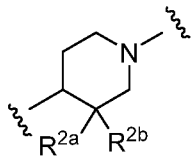
;

R^{3a} is selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



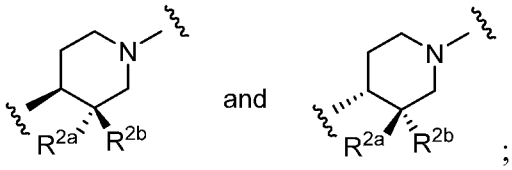
In another embodiment, R^{3a} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, *tert*-butyl, phenyl, and $-CH_2Ph$. In another embodiment, R^{3a} is $-CH_2Ph$.

[0045] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



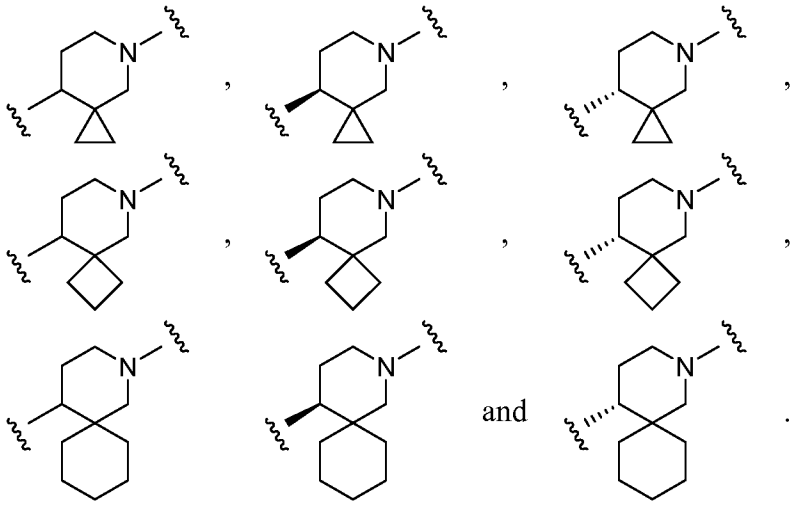
;

R^{2a} and R^{2b} are each independently selected from the group consisting of halo and C_{1-6} alkyl; or R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:

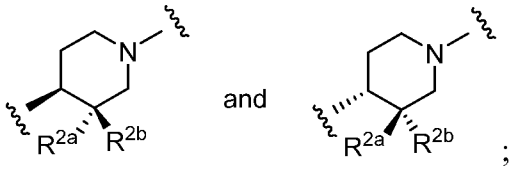


;

and R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl. In another embodiment, B is selected from the group consisting of:



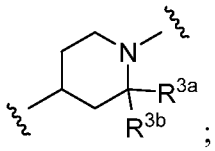
In another embodiment, B is selected from the group consisting of:



;

and R^{2a} and R^{2b} are each independently selected from the group consisting of halo and C_{1-4} alkyl. In another embodiment, R^{2a} and R^{2b} are selected from the group consisting of fluoro and methyl.

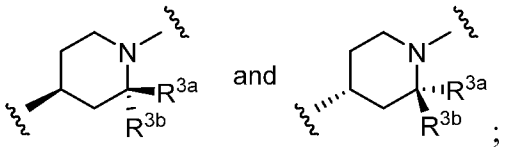
[0046] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



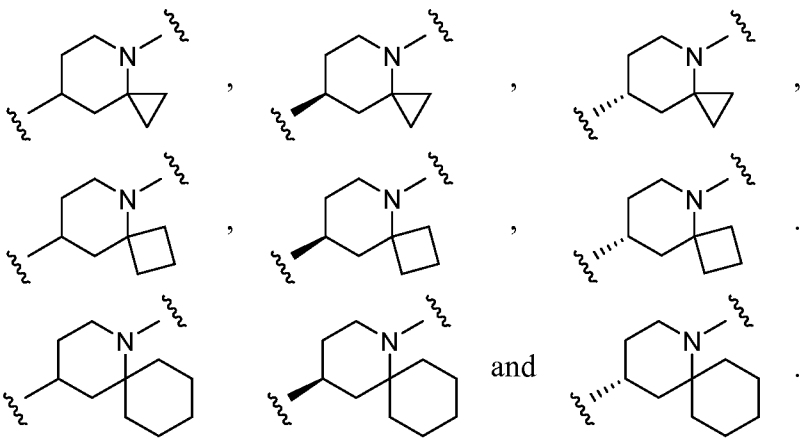
;

R^{3a} and R^{3b} are each independently selected from the group consisting of halo and C_{1-6} alkyl; or

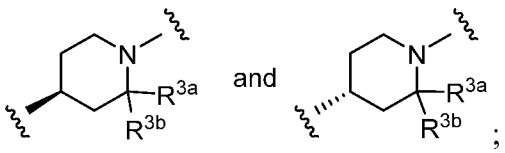
R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



and R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl. In another embodiment, B is selected from the group consisting of:



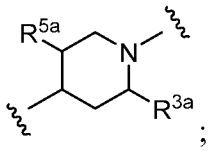
In another embodiment, B is selected from the group consisting of:



;

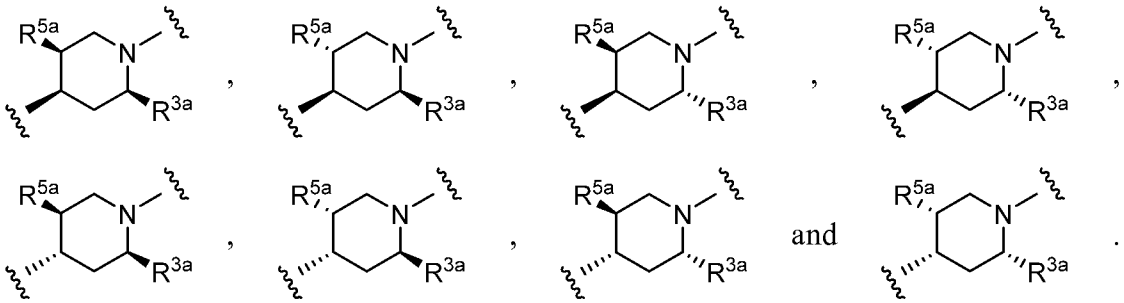
and R^{3a} and R^{3b} are each independently selected from the group consisting of halo and C_{1-4} alkyl. In another embodiment, R^{3a} and R^{3b} are selected from the group consisting of fluoro and methyl.

[0047] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



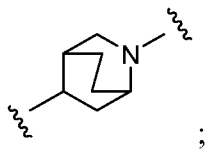
;

R^{3a} and R^{5a} are each independently C_{1-6} alkyl; or R^{3a} and R^{5a} taken together form a C_{1-4} bridge; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



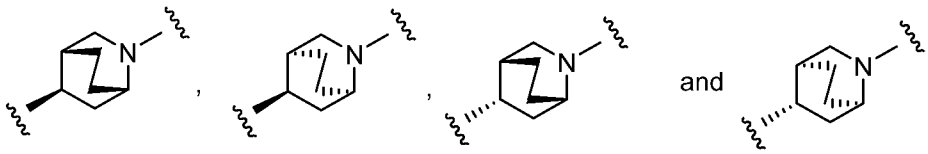
In another embodiment, R^{3a} and R^{5a} are each independently C_{1-4} alkyl. In another embodiment, R^{3a} and R^{5a} are each methyl or ethyl.

[0048] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:

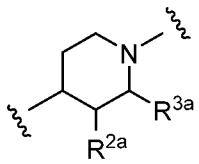


;

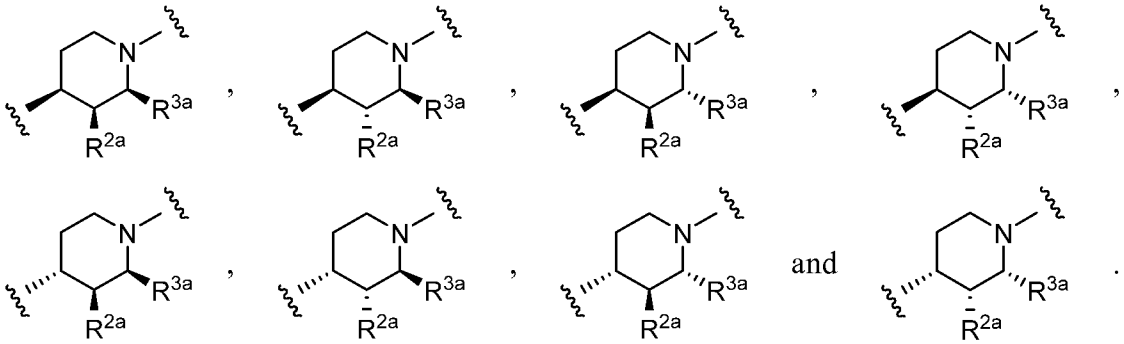
and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



[0049] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:

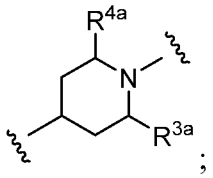


R^{2a} and R^{3a} are each independently C_{1-6} alkyl; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is:

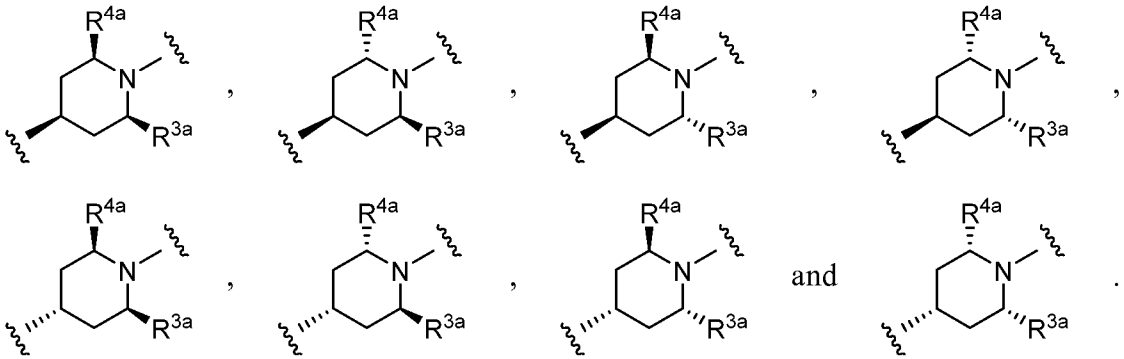


In another embodiment, R^{2a} and R^{3a} are each independently C_{1-4} alkyl. In another embodiment, R^{2a} and R^{3a} are each methyl or ethyl.

[0050] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:

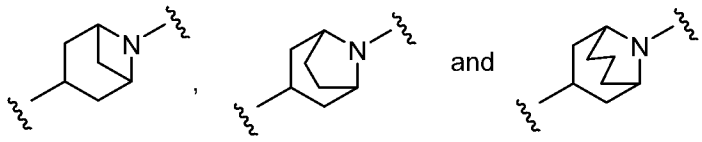


R^{3a} and R^{4a} are each independently C_{1-6} alkyl; or R^{3a} and R^{4a} taken together form a C_{1-4} bridge; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is:

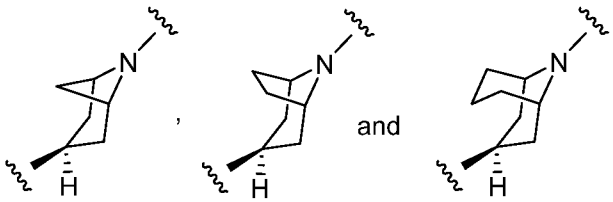


In another embodiment, R^{3a} and R^{4a} are each independently C_{1-4} alkyl. In another embodiment, R^{3a} and R^{4a} are each methyl or ethyl.

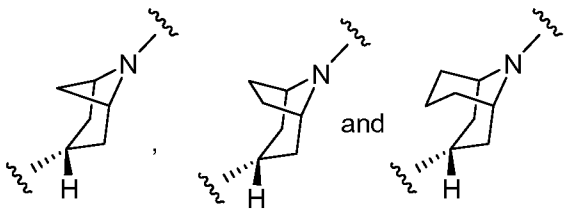
[0051] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is selected from the group consisting of:



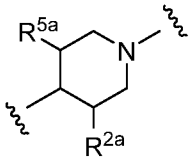
and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is selected from the group consisting of:



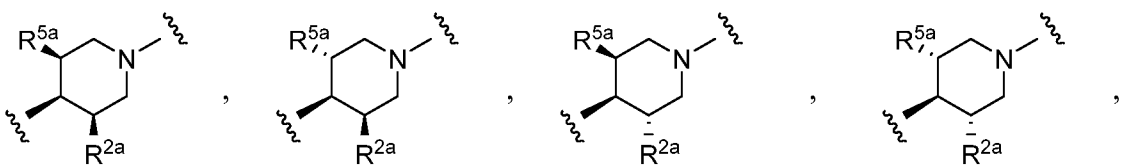
In another embodiment, B is selected from the group consisting of:

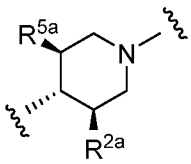
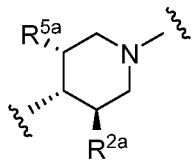
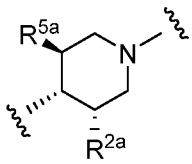
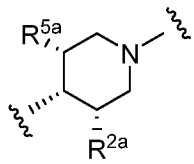


[0052] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein B is:



R^{2a} and R^{5a} are each independently selected from the group consisting of C_{1-6} alkyl and alkoxycarbonyl; or R^{2a} and R^{5a} taken together form a C_{1-4} bridge; and R^1, X, and Z are as defined above in connection with Formula **I**. In another embodiment, B is:






and


In another embodiment, R^{2a} and R^{5a} are each independently selected from the group consisting of C_{1-4} alkyl and alkoxycarbonyl. In another embodiment, R^{2a} and R^{5a} are each independently selected from the group consisting of methyl and $-CO_2Me$.

[0053] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is $-S(=O)_2-$ and R^1, B, and Z are as defined above in connection with Formula **I**.

[0054] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is -C(=O)- and R^1, B, and Z are as defined above in connection with Formula **I**.

[0055] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is absent and R^1, B, and Z are as defined above in connection with Formula **I**.

[0056] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is $-S(=O)_2N(H)-$ and R^1, B, and Z are as defined above in connection with Formula **I**.

[0057] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is -C(=O)N(H)- and R^1, B, and Z are as defined above in connection with Formula **I**.

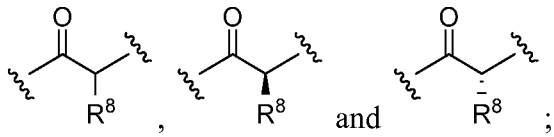
[0058] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is -C(=O)O- and R^1, B, and Z are as defined above in connection with Formula **I**.

[0059] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates,

thereof, wherein X is -S(=O)$_2$CH$_2$- and R^1, B, and Z are as defined above in connection with Formula **I**.

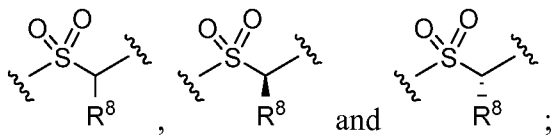
[0060] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is -C(=O)CH$_2$- and R^1, B, and Z are as defined above in connection with Formula **I**.

[0061] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is selected from the group consisting of:



R^8 is selected from the group consisting of C$_{1-4}$ alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and -N(R^9)C(=O)R^{10}; and R^1, R^9, R^{10}, B, and Z are as defined above in connection with Formula **I**. In another embodiment, R^8 is selected from the group consisting of -NH$_2$, -CH$_2$NH$_2$, and -N(H)C(=O)R^{10}.

[0062] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein X is selected from the group consisting of:

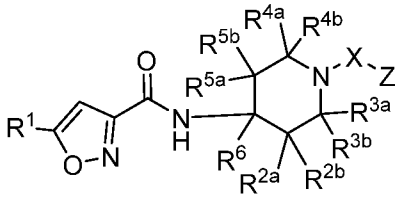


R^8 is selected from the group consisting of C$_{1-4}$ alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and -N(R^9)C(=O)R^{10}; and R^1, R^9, R^{10}, B, and Z are as defined above in connection with Formula **I**. In another embodiment, R^8 is selected from the group consisting of -NH$_2$, -CH$_2$NH$_2$, and -N(H)C(=O)R^{10}.

[0063] In another embodiment, Compounds of the Disclosure are compounds having Formula **I**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, (aralkylamino)alkyl, optionally substituted C$_{6-14}$ aryl, optionally substituted 4- to 14-membered heterocyclo,

optionally substituted 5- to 14-membered heteroaryl, and optionally substituted C_{3-12} cycloalkyl.

[0064] In another embodiment, Compounds of the Disclosure are compounds having Formula **II**:



II

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein

[0065] R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or

[0066] R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0067] R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0068] R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0069] R^{5a} and R^{5b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0070] R^{2a} and R^{5a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0071] R^{3a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0072] R^{2a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0073] R^{3a} and R^{5a} taken form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

[0074] R^6 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

[0075] with the proviso that a) one or more of R^{2a}, R^{3a}, R^{4a}, and R^{5a} is independently selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or b) R^6 is C_{1-4} alkyl; and

[0076] R^1, X, and Z are as defined in connection with Formula **I**.

[0077] In another embodiment, Compounds of the Disclosure are compounds having Formula **II**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is selected from the group consisting of optionally substituted C_{1-6} alkyl, fluoroalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and heteroaralkyl, when X is absent.

[0078] In another embodiment, Compounds of the Disclosure are compounds having Formula **II**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein

[0079] R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or

[0080] R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

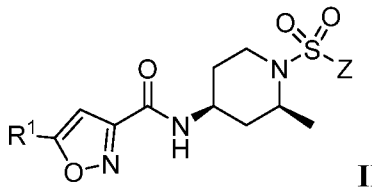
[0081] R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0082] R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

[0083] R^{5a} and R^{5b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; and

[0084] R^1, R^6, X, and Z are as defined in connection with Formula **I**.

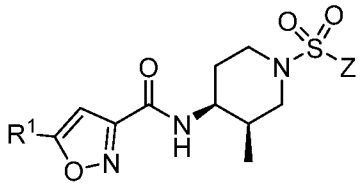
[0085] In another embodiment, Compounds of the Disclosure are compounds having Formula **III**:



III

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, and optionally substituted 4- to 14-membered heterocyclo.

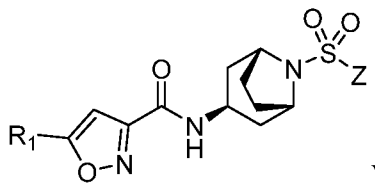
[0086] In another embodiment, Compounds of the Disclosure are compounds having Formula **IV**:



IV

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, and optionally substituted 4- to 14-membered heterocyclo.

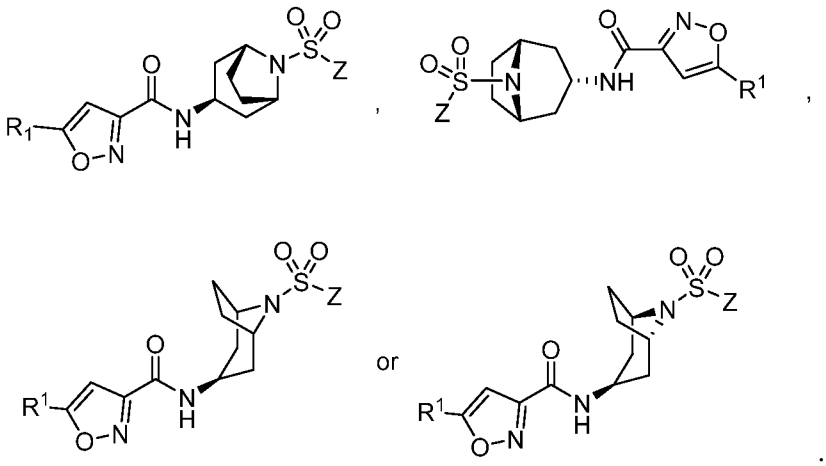
[0087] In another embodiment, Compounds of the Disclosure are compounds having Formula **V**:



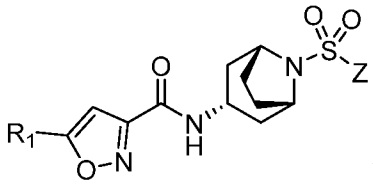
V

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment,

Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C_{3-12} cycloalkyl. It will be understood by those of ordinary skill in the art that compounds having Formula **V** can be drawn in various ways, *e.g.*,

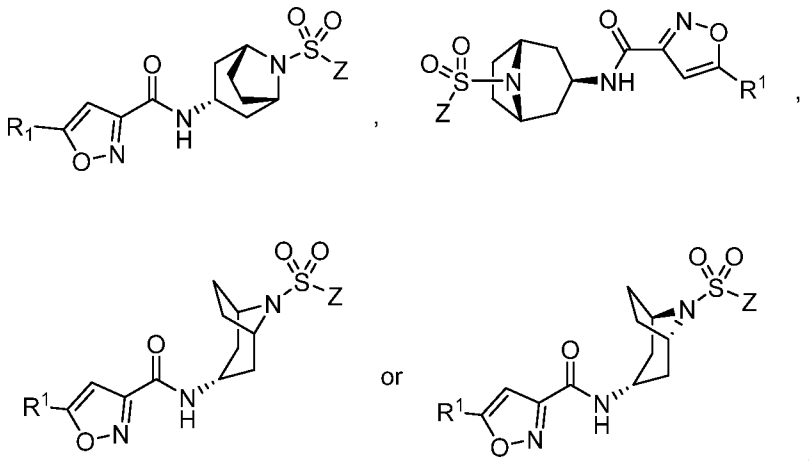


[0088] In another embodiment, Compounds of the Disclosure are compounds having Formula **VI**:

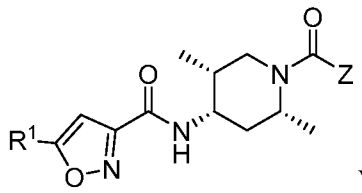


VI

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C_{3-12} cycloalkyl. It will be understood by those of ordinary skill in the art that compounds having Formula **VI** can be drawn in various ways, *e.g.*,



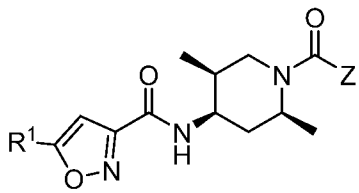
[0089] In another embodiment, Compounds of the Disclosure are compounds having Formula **VII**:



VII

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C_{3-12} cycloalkyl.

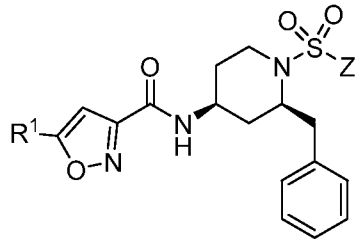
[0090] In another embodiment, Compounds of the Disclosure are compounds having Formula **VIII**:



VIII

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**. In another embodiment, Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, and optionally substituted C_{3-12} cycloalkyl.

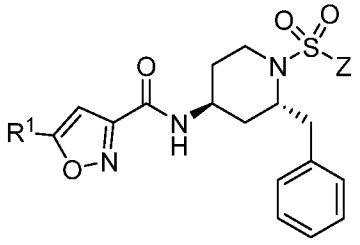
[0091] In another embodiment, Compounds of the Disclosure are compounds having Formula **IX**:



IX

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**.

[0092] In another embodiment, Compounds of the Disclosure are compounds having Formula **X**:



X

and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z and R^1 are as defined above in connection with Formula **I**.

[0093] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is ethyl.

[0094] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is ethyl and Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

[0095] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is n-propyl.

[0096] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is n-propyl and Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

[0097] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is isopropyl.

[0098] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is isopropyl and Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

[0099] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is isobutyl.

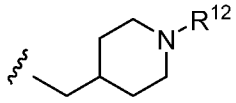
[0100] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is isobutyl and Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

[0101] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is cyclopropyl.

[0102] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is cyclopropyl and Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

[0103] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is (heterocyclo)alkyl.

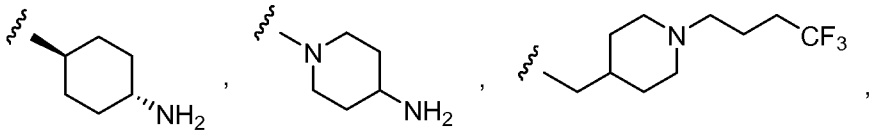
[0104] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is a (heterocyclo)alkyl having the following structure:



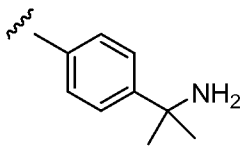
;

wherein R^{12} is selected from the group consisting of hydrogen, fluoroalkyl, hydroxyalkyl, aralkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In another embodiment, R^{12} is selected from the group consisting of hydrogen, fluoroalkyl, hydroxyalkyl, aralkyl, alkyl, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

[0105] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein Z is selected from the group consisting of:

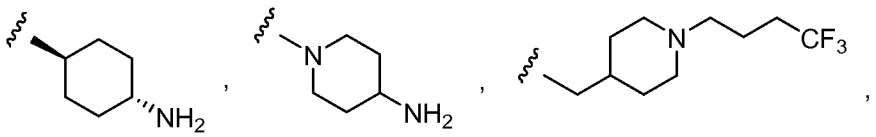


and

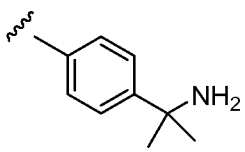


.

[0106] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-X**, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein R^1 is cyclopropyl and Z is selected from the group consisting of:



and



.

[0107] In another embodiment, Compounds of the Disclosure are compounds of Table 1, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof,

or a different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 1 are provided in Table 1A.

[0108] In another embodiment, Compounds of the Disclosure are compounds of Table 2, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or a different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 2 are provided in Table 2A.

[0109] In another embodiment, Compounds of the Disclosure are compounds of Table 3, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or a different pharmaceutically acceptable salt thereof. The chemical names of the compounds of Table 3 are provided in Table 3A.

[0110] In another embodiment, Compounds of the Disclosure are compounds of Tables 1 and 2, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or a different pharmaceutically acceptable salt thereof.

[0111] In another embodiment, Compounds of the Disclosure are compounds of Tables 1, 2, and 3, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or a different pharmaceutically acceptable salt thereof.

[0112] In another embodiment, Compounds of the Disclosure are compounds of Tables 1, 1A, 2, 2A, 3, and 3A, and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, or a different pharmaceutically acceptable salt thereof.

[0113] In another embodiment, Compounds of the Disclosure are selected from the group consisting of:

[0114] N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0115] N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0116] N-((2S,4S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0117] N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0118] 5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide; and

[0119] N-((1R,3r,5S)-8-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide,

[0120] and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof.

[0121] In another embodiment, Compounds of the Disclosure are selected from the group consisting of:

[0122] N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0123] N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

[0124] N-((2S,4S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

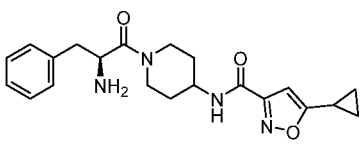
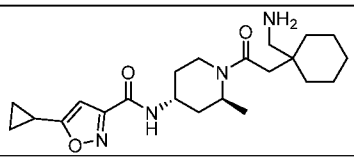
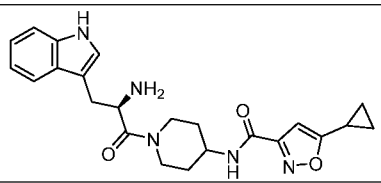
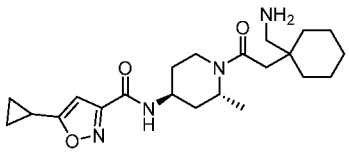
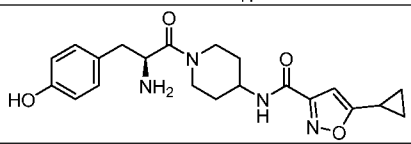
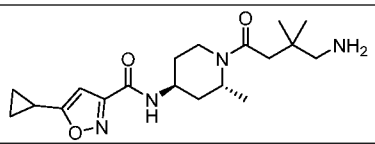
[0125] N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide; and

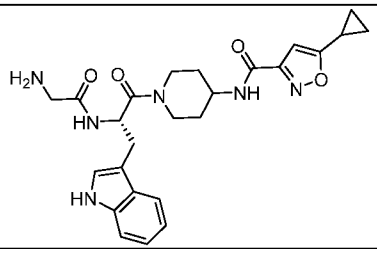
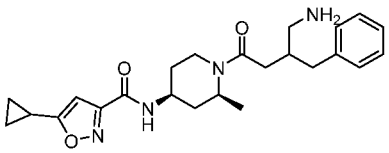
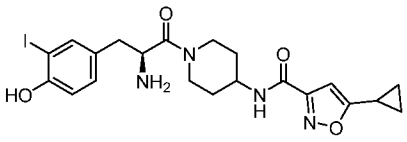
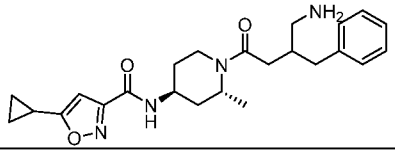
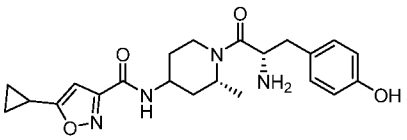
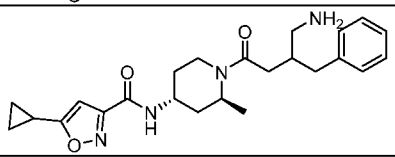
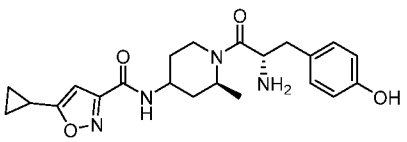
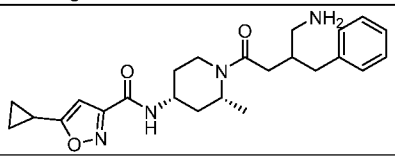
[0126] 5-cyclopropyl-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide,

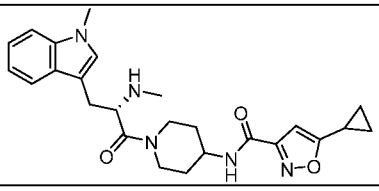
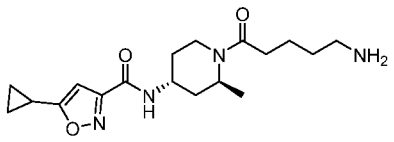
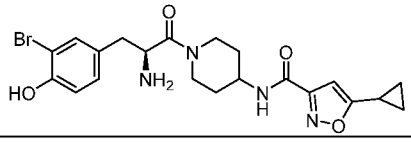
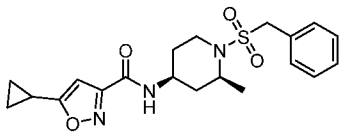
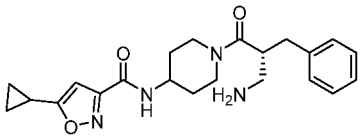
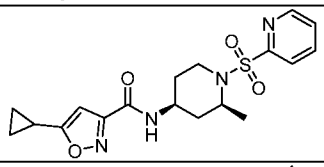
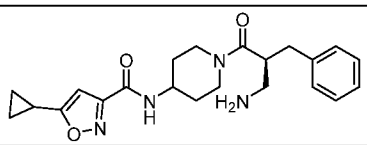
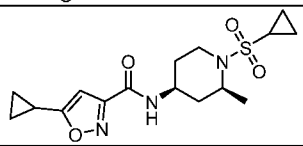
[0127] and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof.

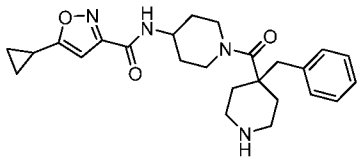
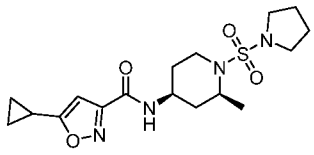
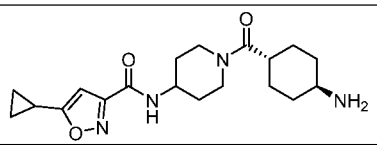
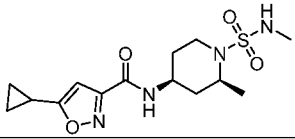
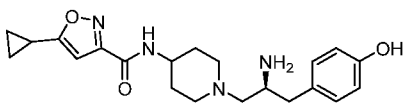
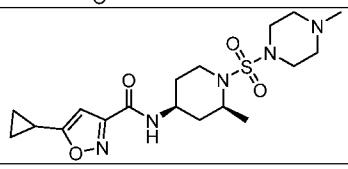
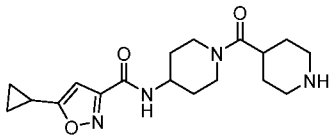
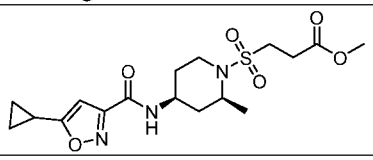
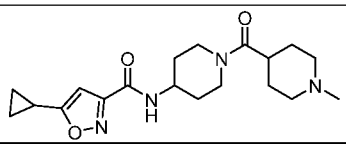
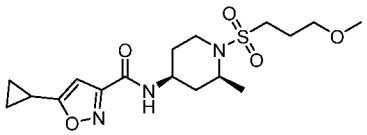
[0128] It should be appreciated that the Compounds of the Disclosure in certain embodiments are the free base, various salts, and hydrate forms, and are not limited to the particular salt listed in Table 1, Table 2, or Table 3.

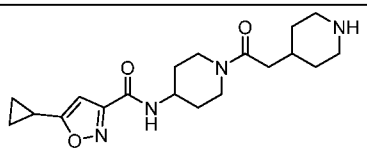
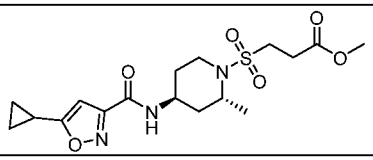
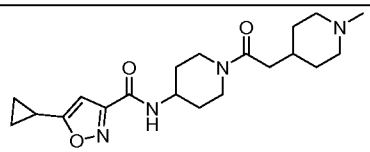
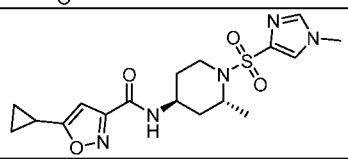
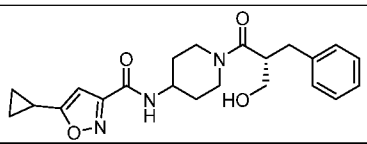
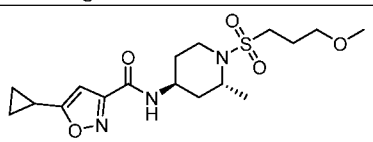
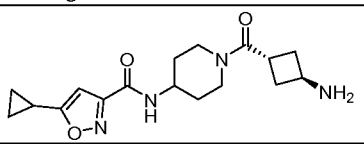
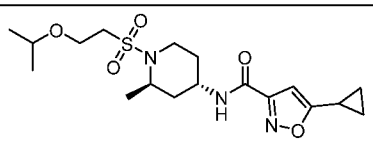
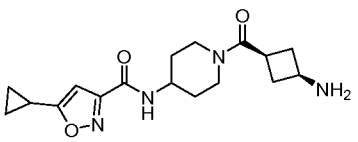
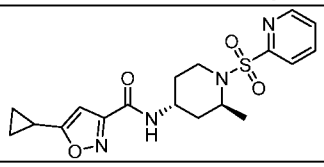
Table 1

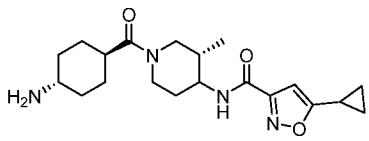
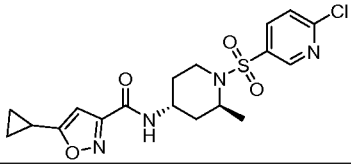
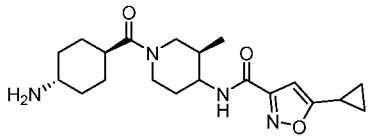
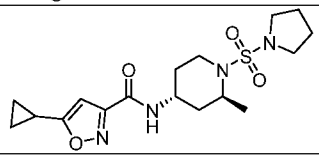
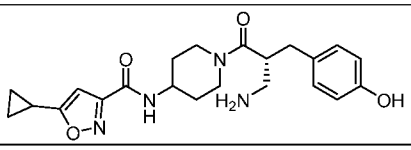
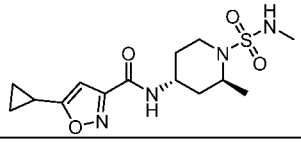
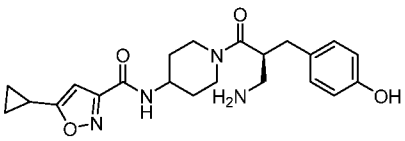
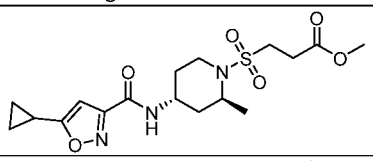
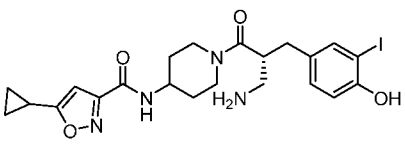
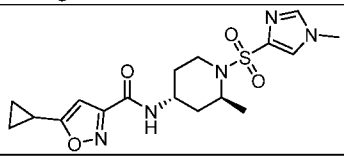
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
1		HCl	**266**		TFA
2		HCl	**267**		HCl
3		TFA	**268**		HCl

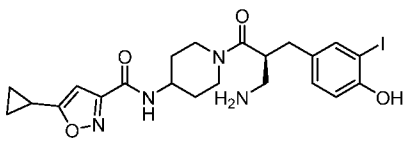
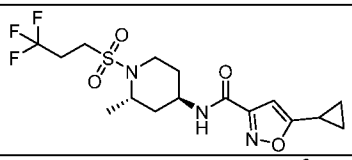
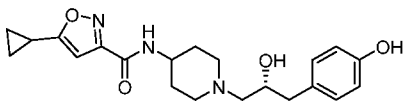
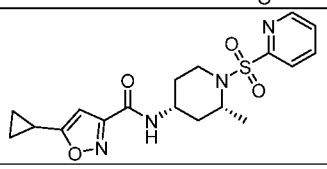
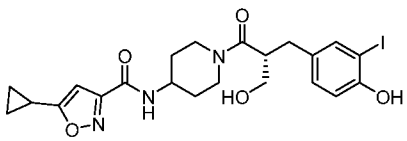
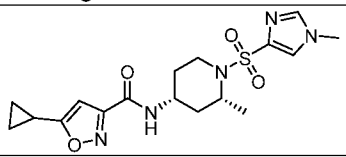
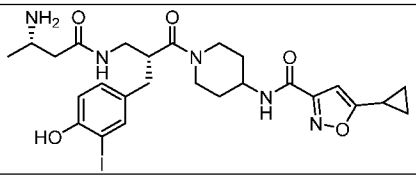
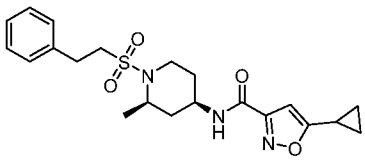
4		TFA	**269**		None
5		TFA	**270**		None
6		HCl	**271**		None
7		HCl	**272**		None

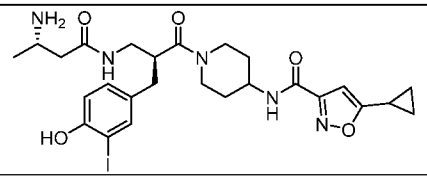
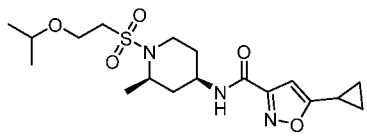
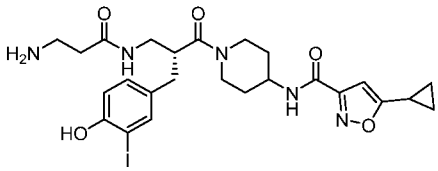
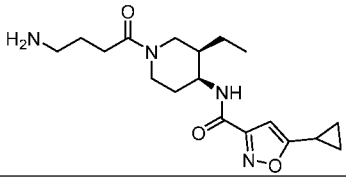
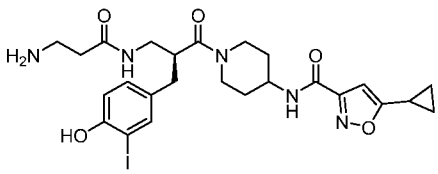
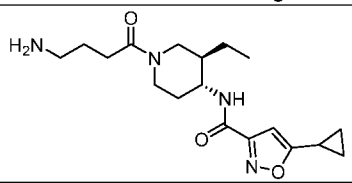
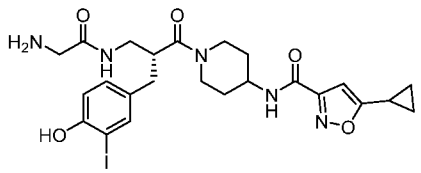
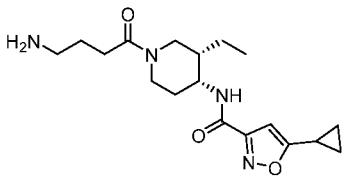
8		TFA	**273**		HCl
9		TFA	**274**		None
10		HCl	**275**		None
11		HCl	**276**		None

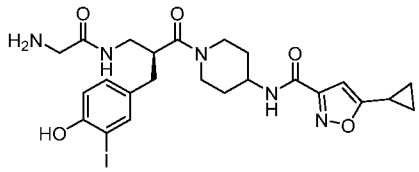
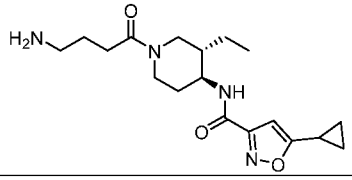
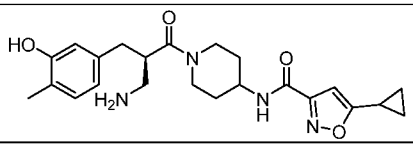
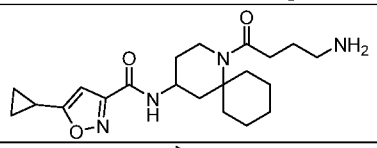
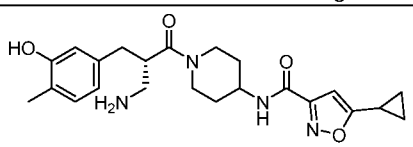
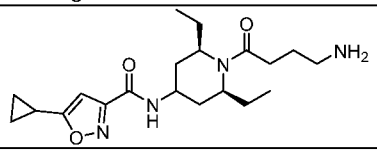
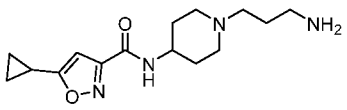
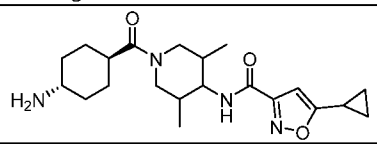
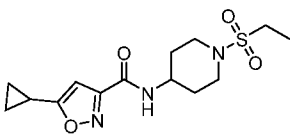
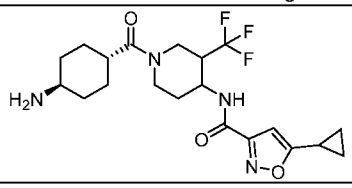
12		TFA	**277**		None
13		HCl	**278**		None
14		HCl	**279**		None
15		HCl	**280**		None
16		None	**281**		HCl

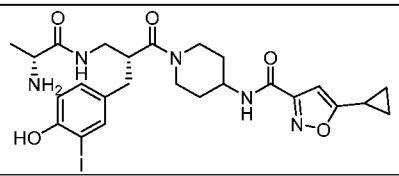
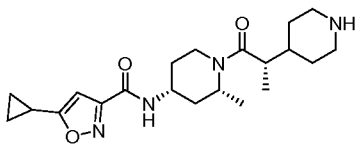
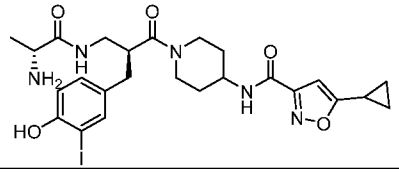
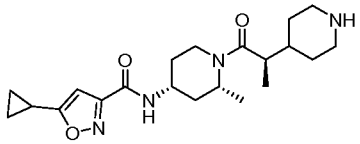
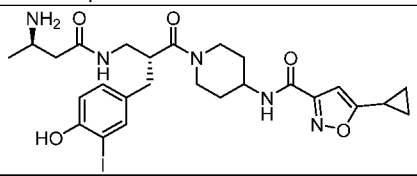
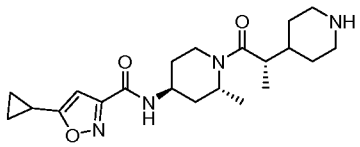
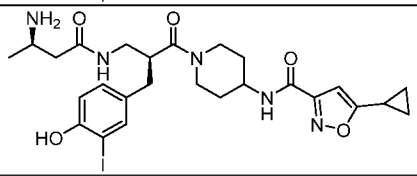
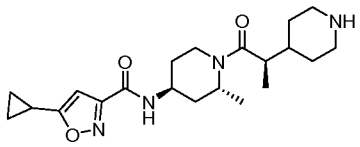
17		HCl	**282**		None
18		None	**283**		None
19		None	**284**		HCl
20		None	**285**		None
21		HCl	**286**		None

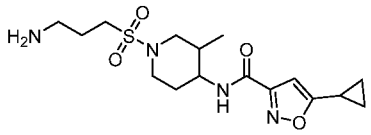
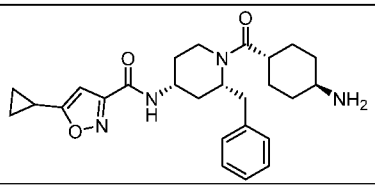
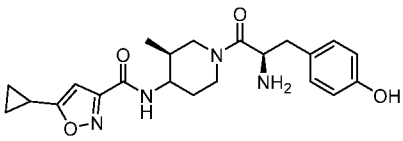
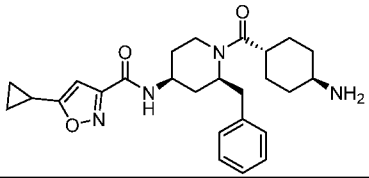
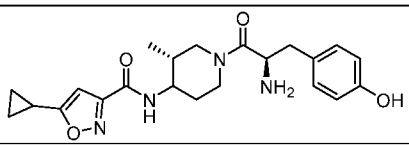
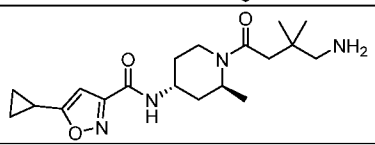
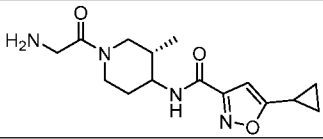
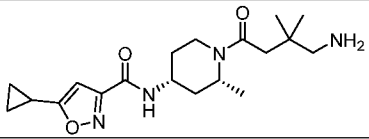
24		HCl	**287**		None
25		HCl	**288**		None
26		HCl	**289**		None
27		None	**290**		None
28		None	**291**		None

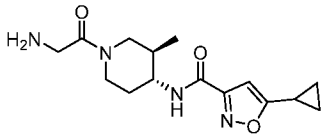
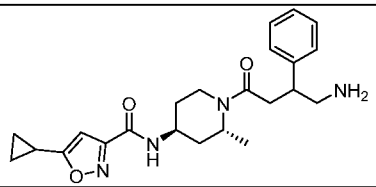
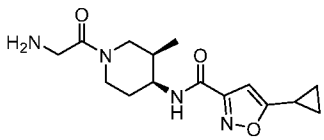
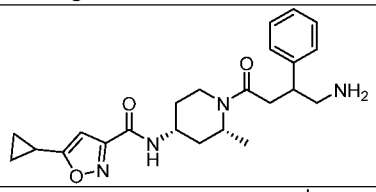
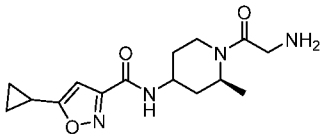
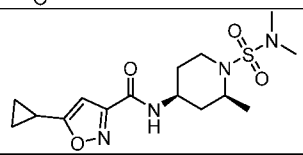
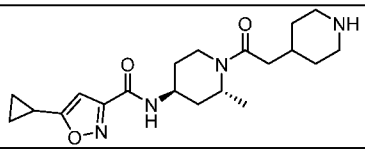
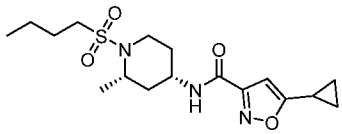
29		None	**292**		HCl
30		None	**293**		TFA
31		None	**294**		HCl
32		HCl	**295**		HCl

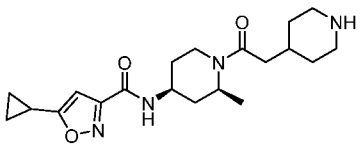
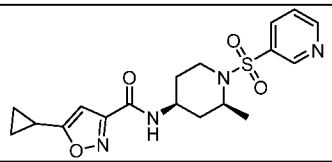
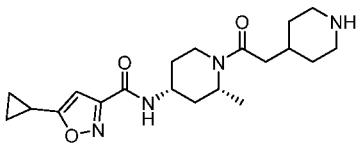
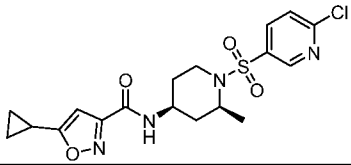
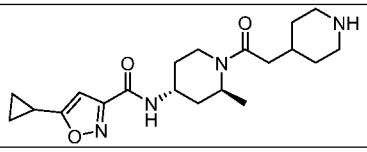
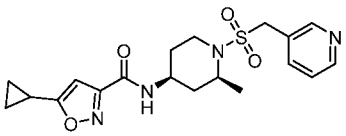
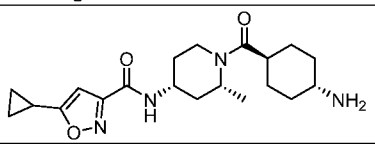
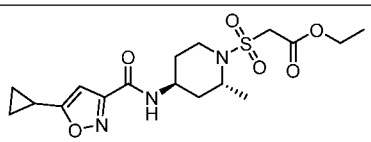
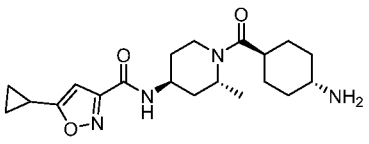
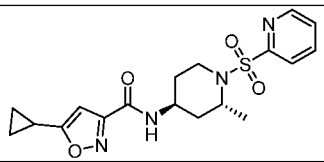
33		HCl	**296**		None
34		HCl	**297**		TFA
35		HCl	**298**		TFA
36		HCl	**299**		TFA

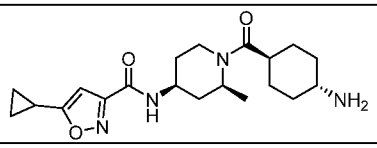
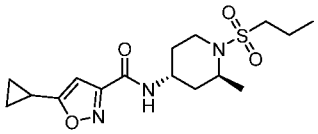
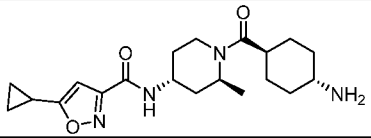
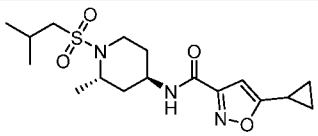
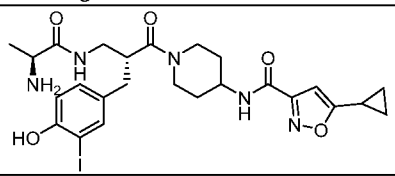
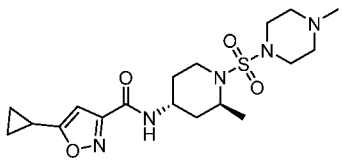
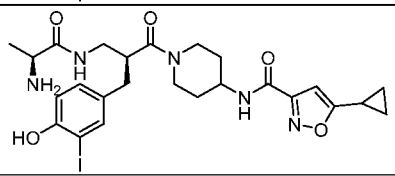
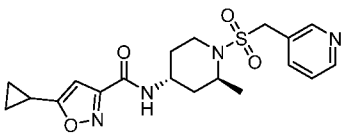
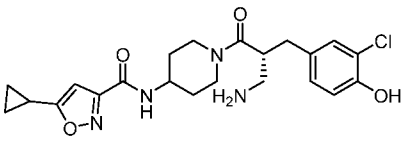
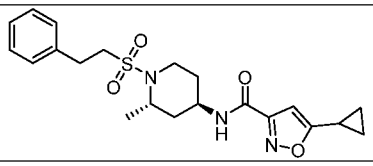
37		HCl	**300**		TFA
38		HCl	**301**		TFA
39		HCl	**302**		TFA
40		HCl	**303**		TFA
41		None	**304**		TFA

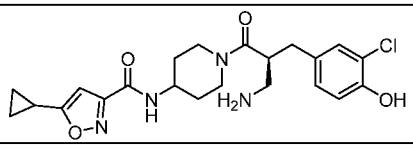
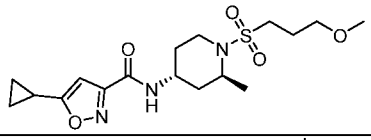
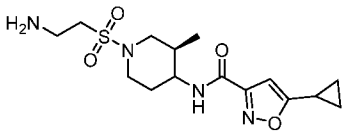
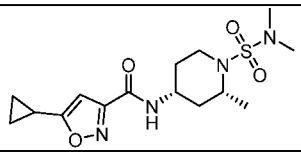
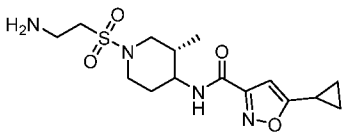
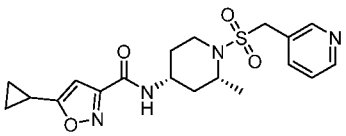
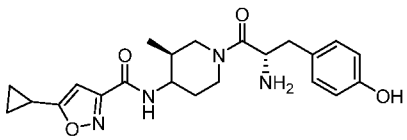
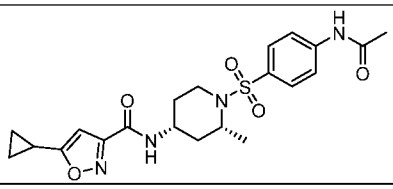
42		HCl	**305**		HCl
43		HCl	**306**		HCl
44		HCl	**307**		HCl
45		HCl	**308**		HCl

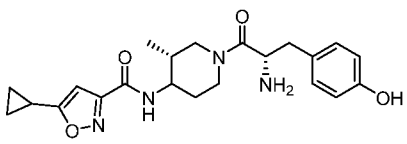
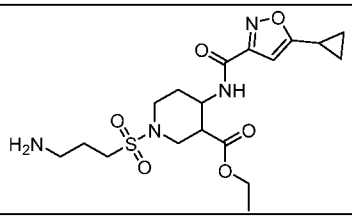
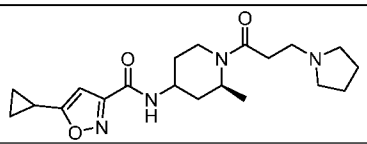
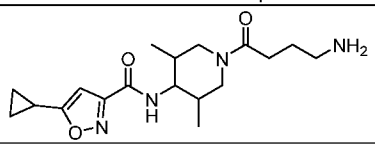
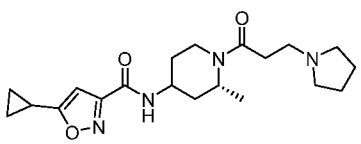
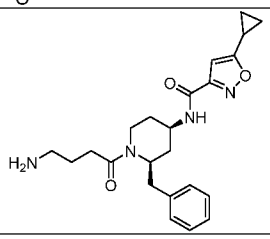
46		None	**309**		HCl
47		HCl	**310**		HCl
48		HCl	**311**		HCl
49		None	**312**		HCl

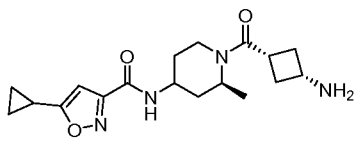
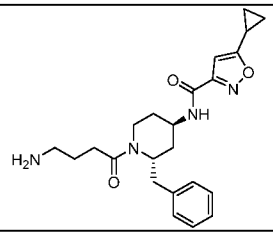
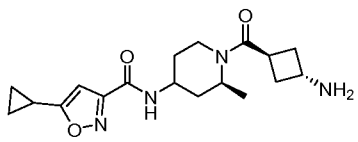
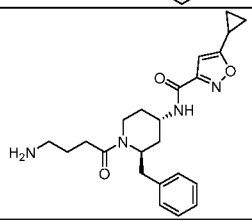
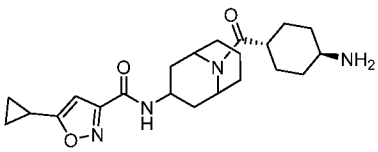
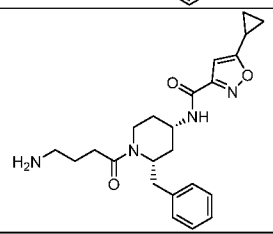
50		None	**313**		HCl
51		None	**314**		HCl
52		HCl	**315**		None
53		HCl	**316**		None

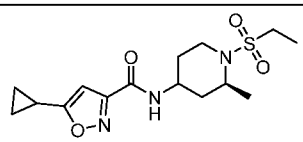
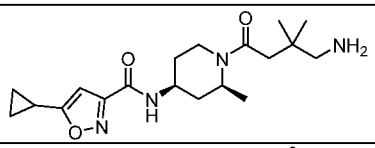
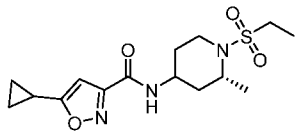
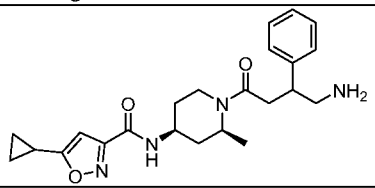
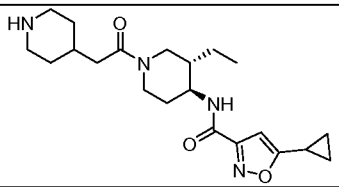
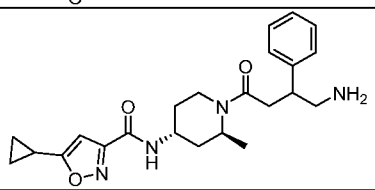
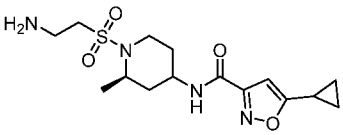
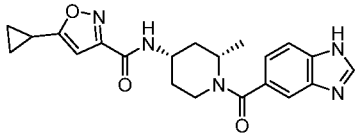
54		HCl	**317**		HCl
55		HCl	**318**		None
56		HCl	**319**		HCl
57		HCl	**320**		None
58		HCl	**321**		None

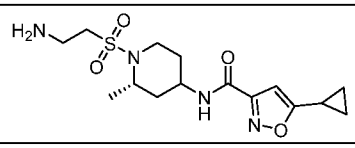
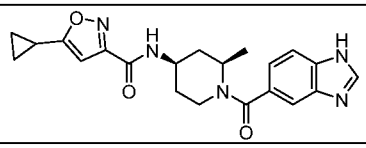
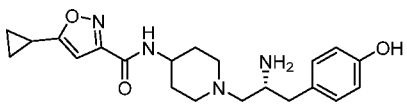
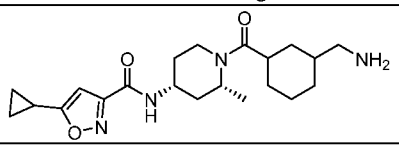
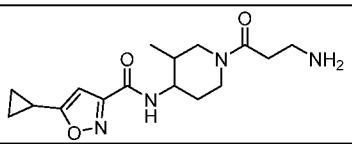
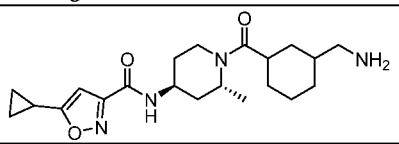
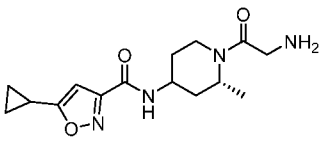
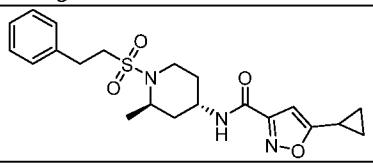
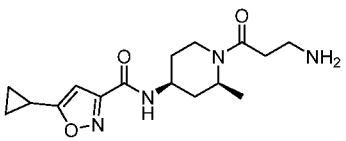
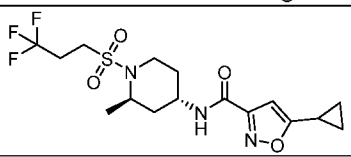
59		HCl	**322**		None
60		HCl	**323**		None
61		None	**324**		None
62		None	**325**		None
63		HCl	**326**		HCl

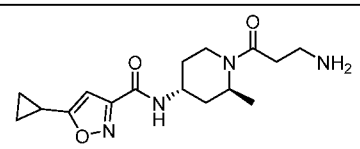
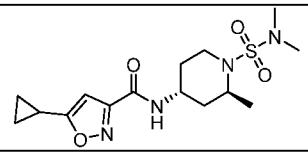
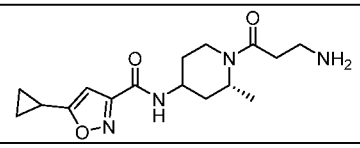
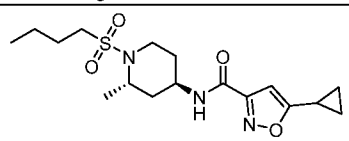
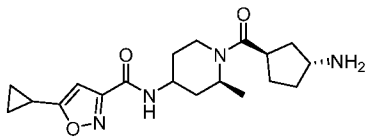
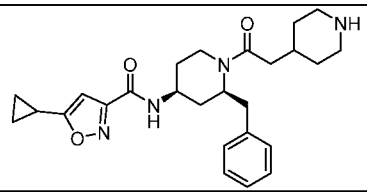
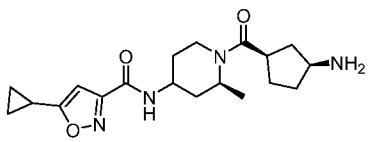
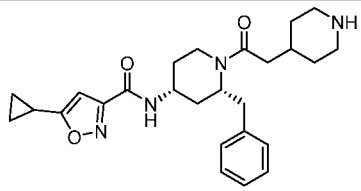
64		None	**327**		None
65		None	**328**		None
66		None	**329**		HCl
67		None	**330**		None

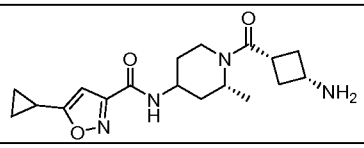
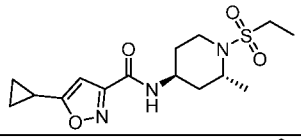
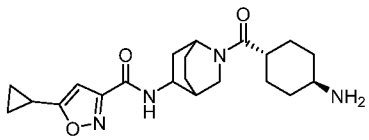
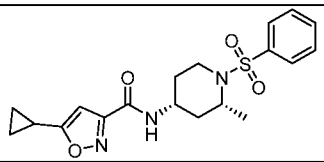
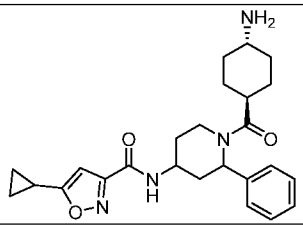
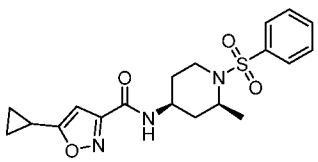
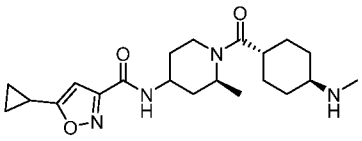
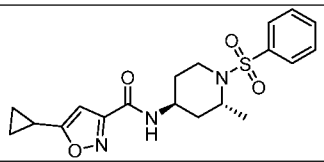
68		None	**331**		TFA
69		None	**332**		TFA
70		None	**333**		HCl

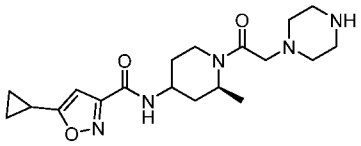
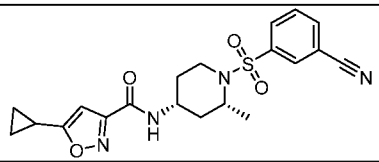
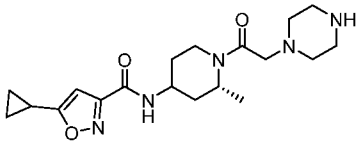
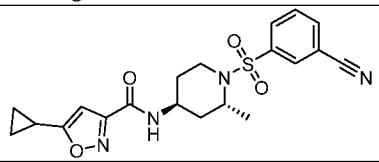
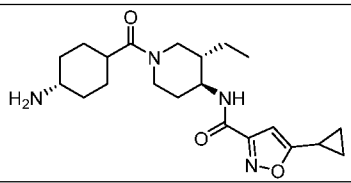
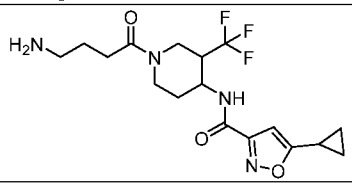
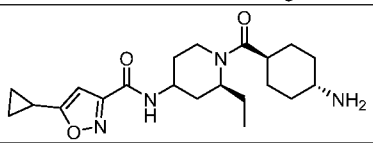
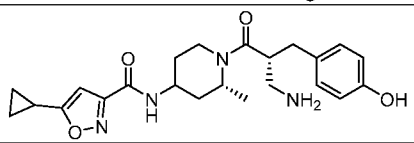
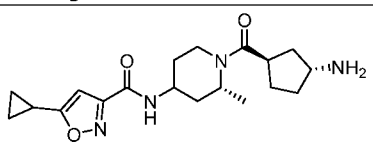
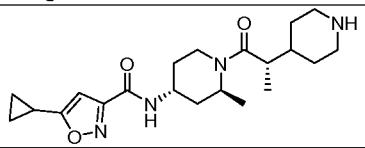
71		HCl	**334**		HCl
72		HCl	**335**		HCl
73		HCl	**336**		HCl

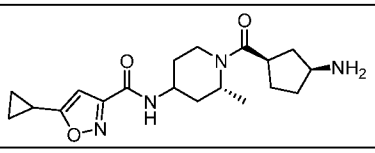
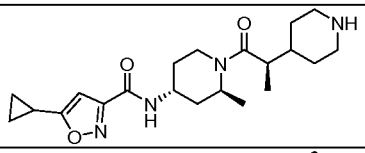
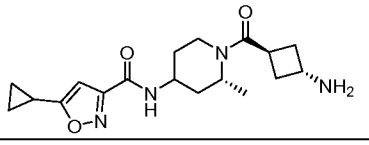
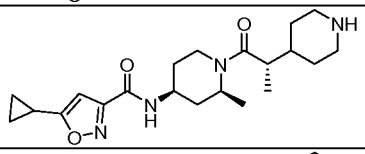
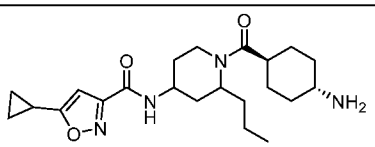
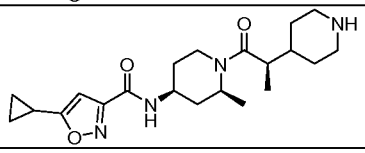
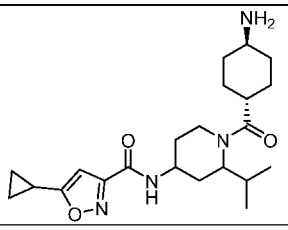
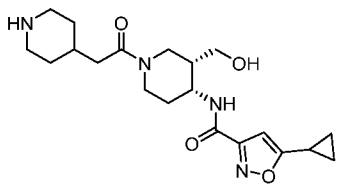
74		None	**337**		TFA
75		None	**338**		TFA
76		HCl	**339**		HCl
77		HCl	**340**		None

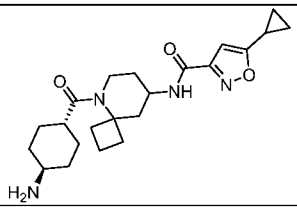
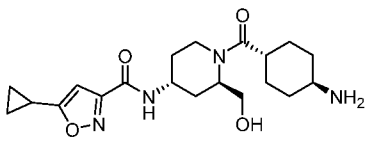
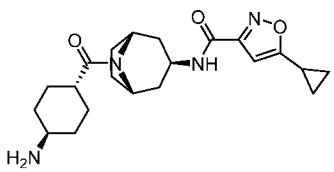
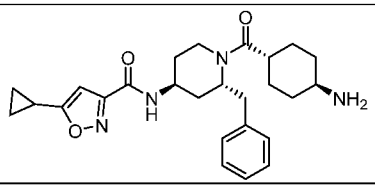
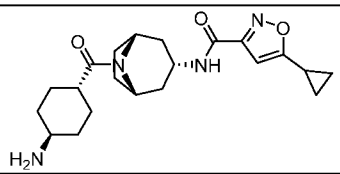
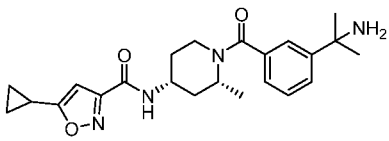
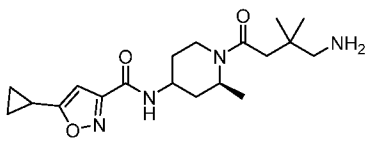
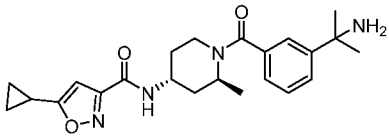
78		HCl	**341**		HCl
79		HCl	**342**		HCl
80		HCl	**343**		HCl
81		HCl	**344**		None
82		HCl	**345**		None

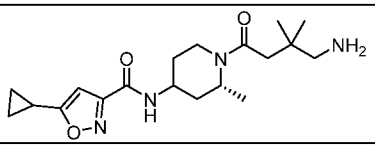
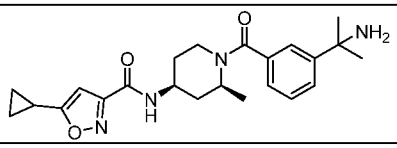
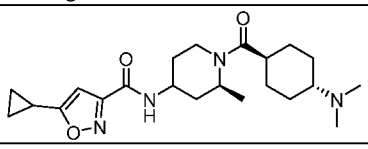
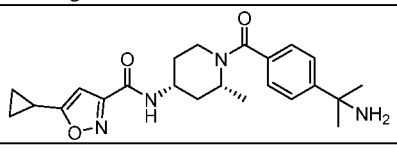
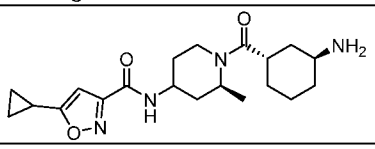
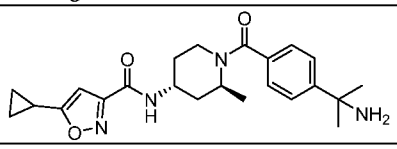
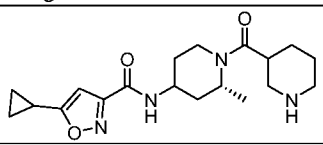
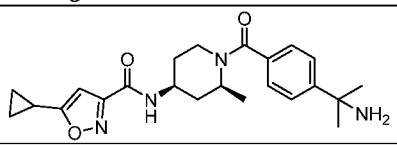
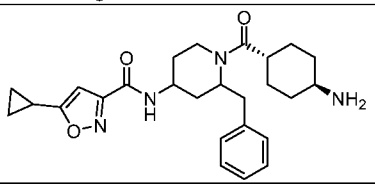
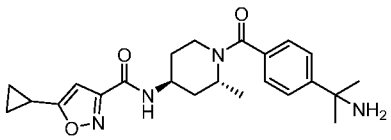
83		HCl	**346**		None
84		None	**347**		None
85		None	**348**		HCl
86		None	**349**		HCl

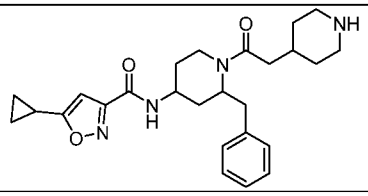
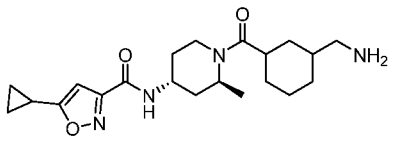
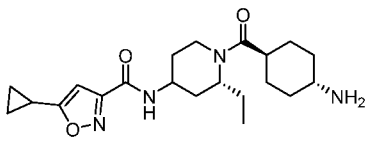
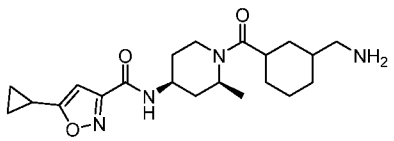
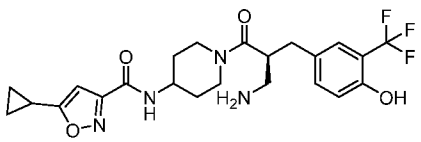
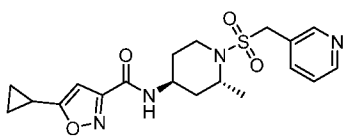
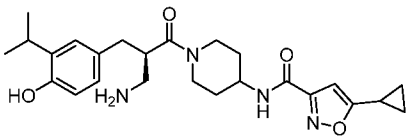
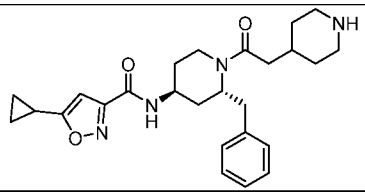
87		HCl	**350**		None
88		HCl	**351**		None
89		HCl	**352**		None
90		None	**353**		None

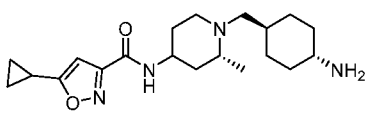
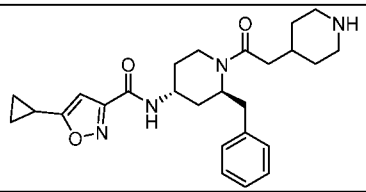
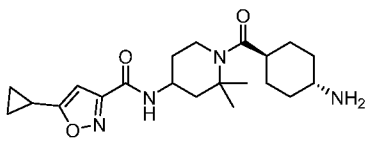
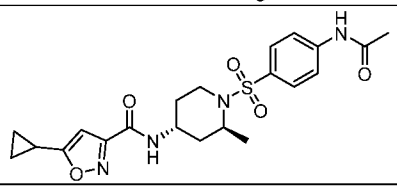
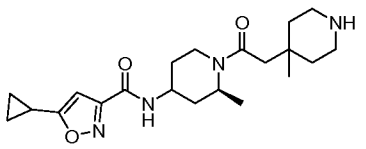
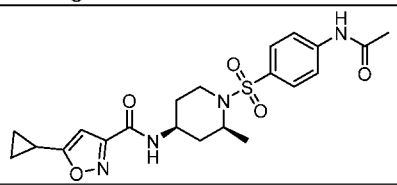
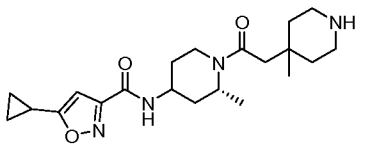
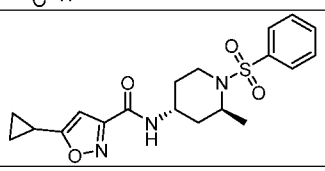
91		None	**354**		None
92		HCl	**355**		None
93		HCl	**356**		TFA
94		None	**357**		HCl
95		HCl	**358**		HCl

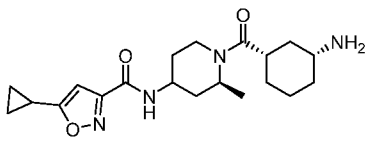
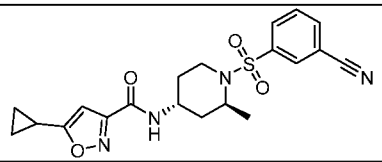
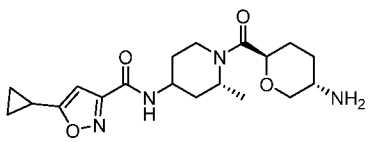
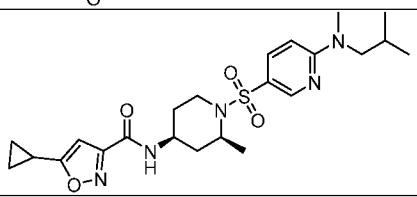
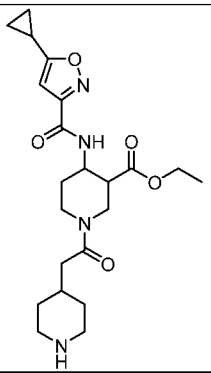
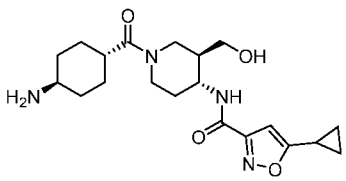
96		HCl	**359**		HCl
97		HCl	**360**		None
98		HCl	**361**		None
99		None	**362**		None

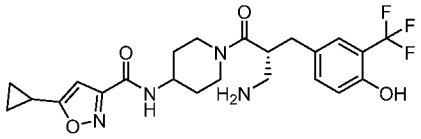
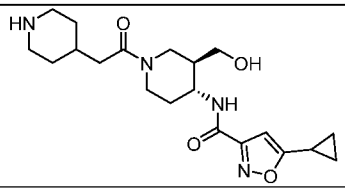
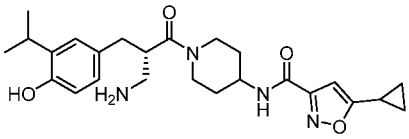
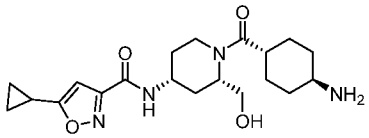
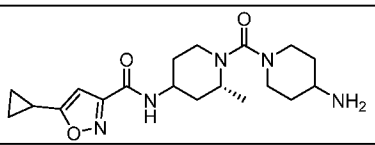
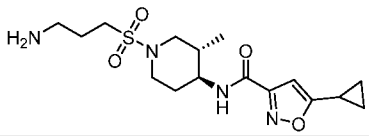
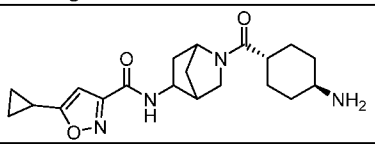
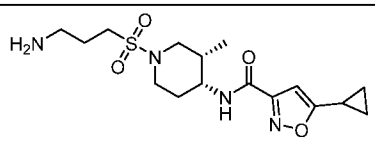
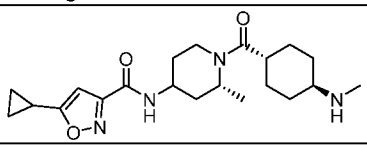
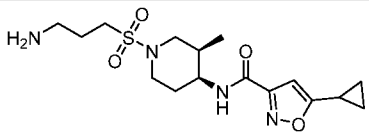
100		None	**363**		TFA
101		None	**364**		HCl
102		None	**365**		HCl
103		HCl	**366**		HCl

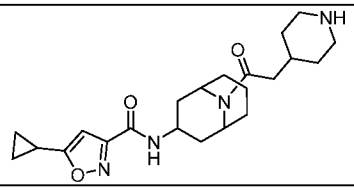
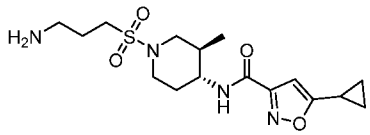
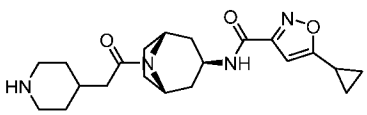
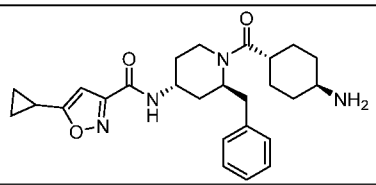
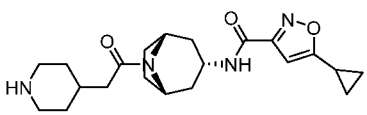
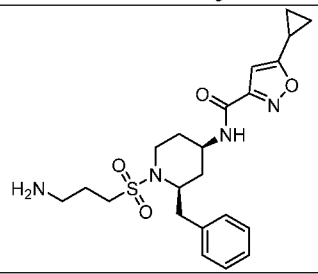
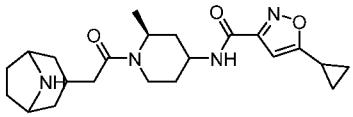
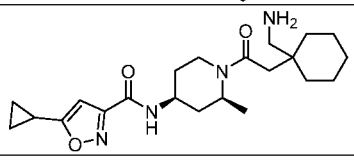
104		None	**367**		HCl
105		None	**368**		HCl
106		HCl	**369**		HCl
107		None	**370**		HCl
108		TFA	**371**		HCl

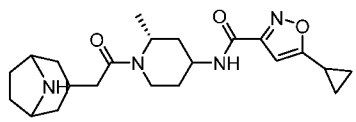
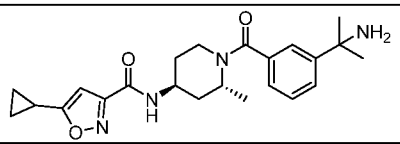
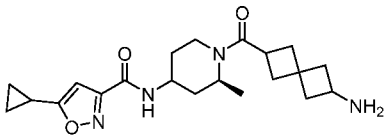
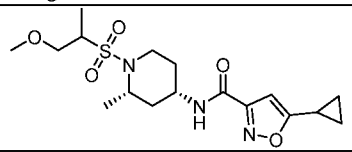
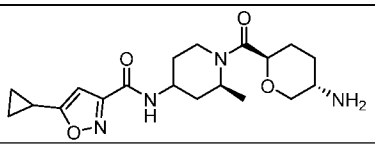
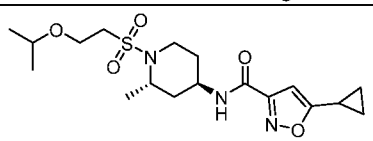
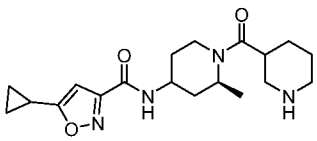
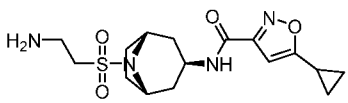
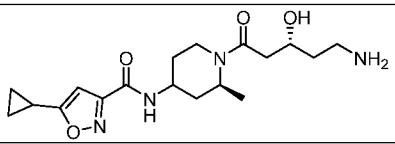
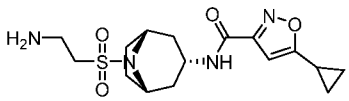
109		TFA	**372**		HCl
110		None	**373**		HCl
111		HCl	**374**		None
112		HCl	**375**		HCl

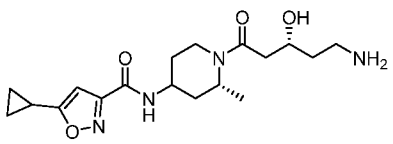
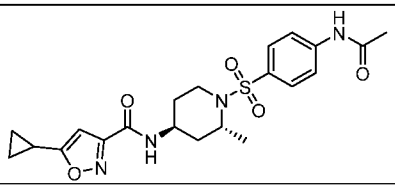
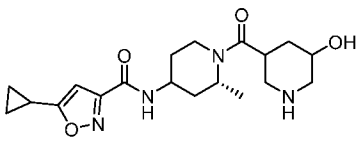
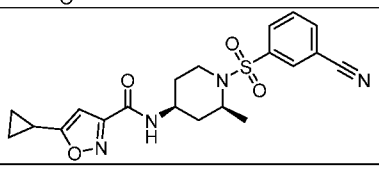
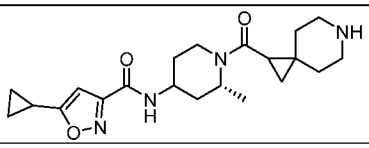
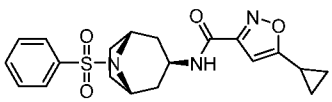
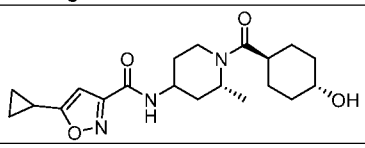
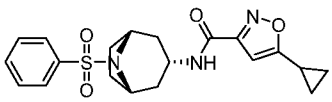
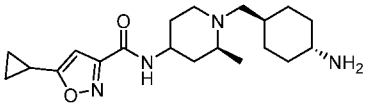
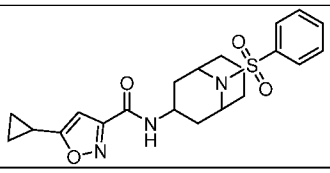
113		HCl	**376**		HCl
114		HCl	**377**		None
115		HCl	**378**		None
116		HCl	**379**		None

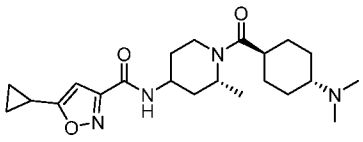
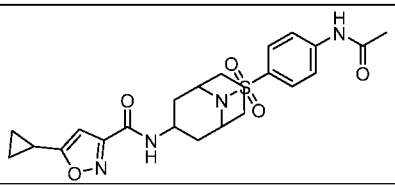
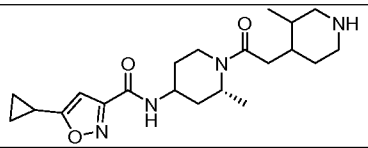
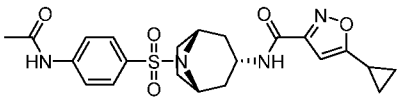
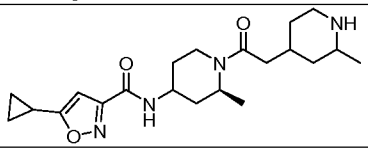
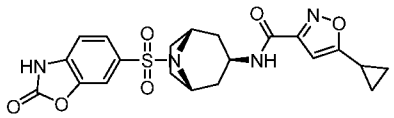
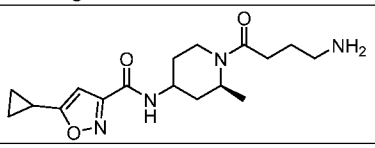
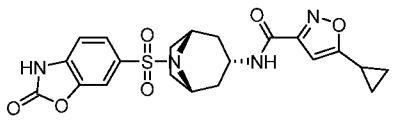
117		HCl	**380**		None
118		HCl	**381**		None
119		TFA	**382**		HCl

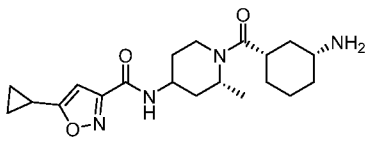
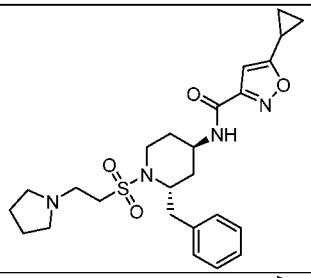
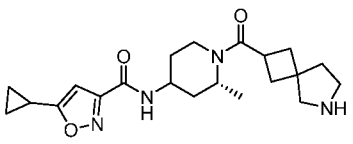
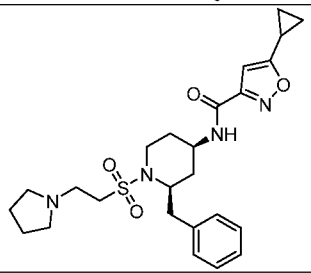
120		TFA	**383**		None
121		HCl	**384**		TFA
122		None	**385**		None
123		HCl	**386**		None
124		None	**387**		None

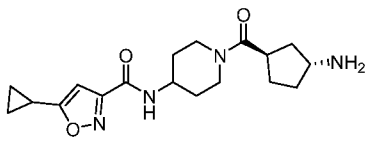
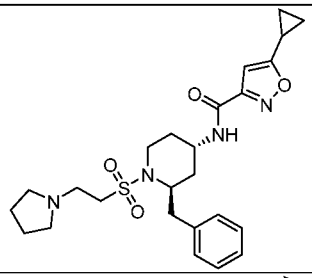
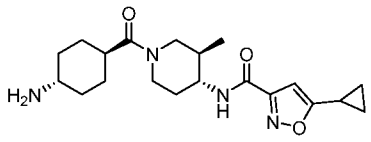
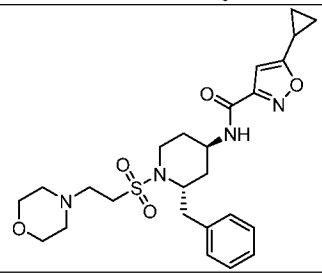
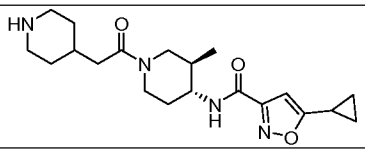
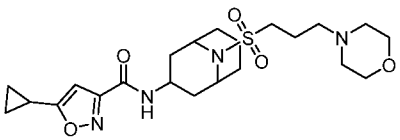
125		HCl	**388**		None
126		HCl	**389**		HCl
127		HCl	**390**		HCl
128		HCl	**391**		TFA

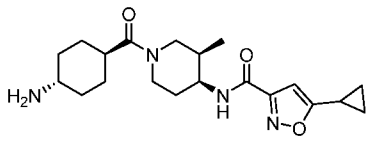
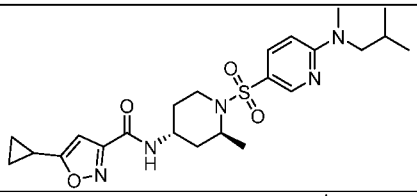
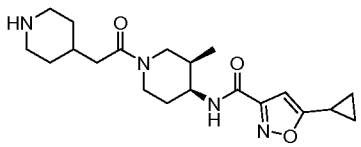
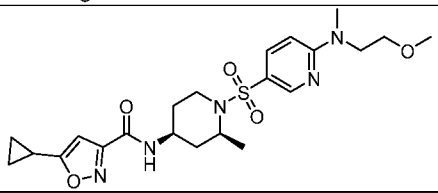
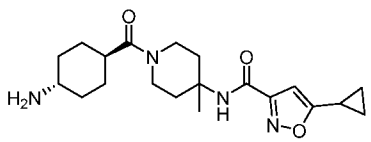
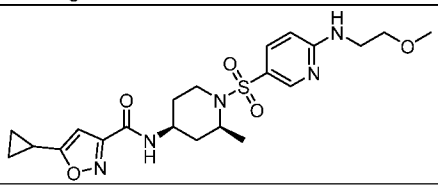
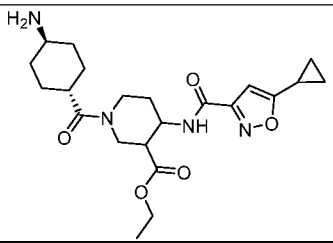
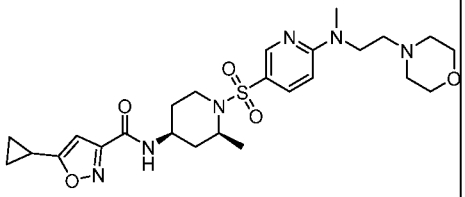
129		HCl	**392**		HCl
130		HCl	**393**		HCl
131		HCl	**394**		None
132		HCl	**395**		None
133		None	**396**		HCl

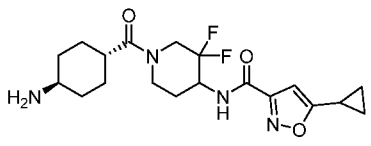
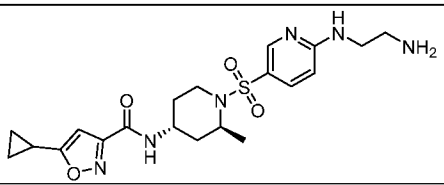
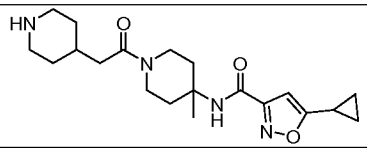
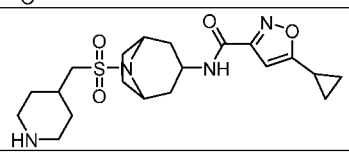
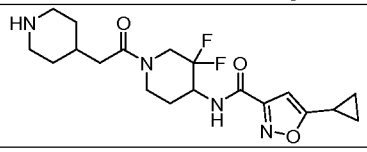
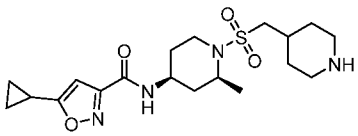
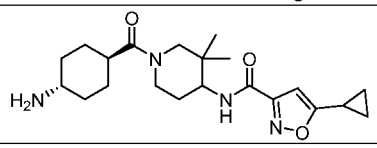
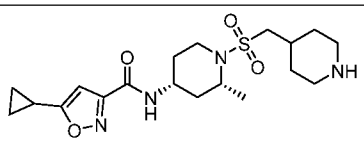
134		None	**397**		None
135		HCl	**398**		None
136		HCl	**399**		None
137		None	**400**		HCl
138		HCl	**401**		None

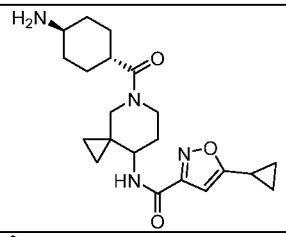
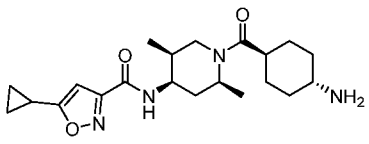
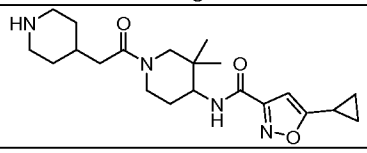
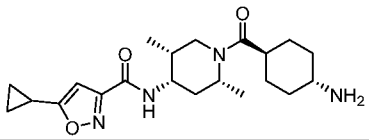
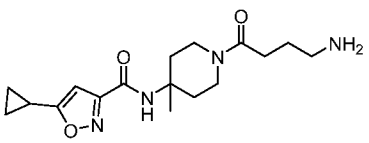
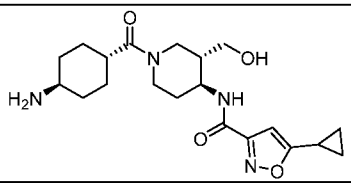
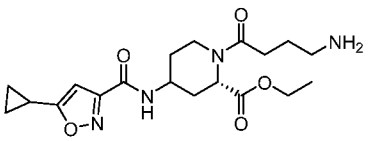
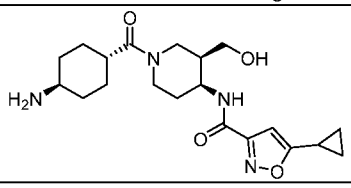
139		HCl	**402**		None
140		None	**403**		None
141		None	**404**		None
142		HCl	**405**		HCl

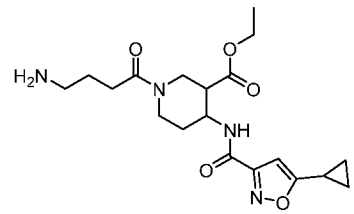
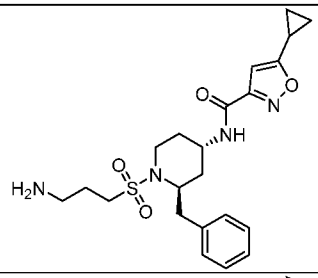
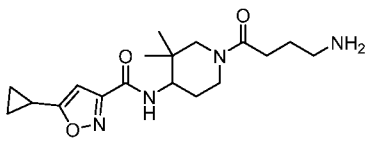
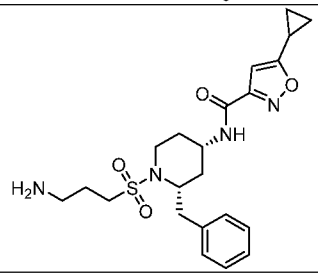
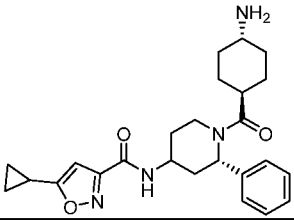
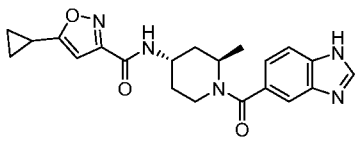
143		HCl	**406**		None
144		None	**407**		None

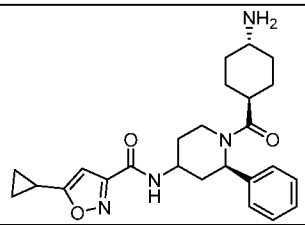
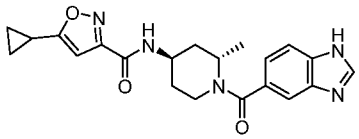
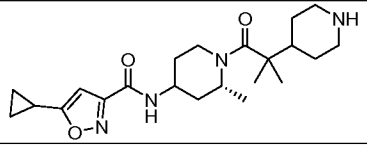
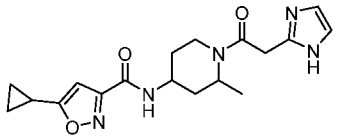
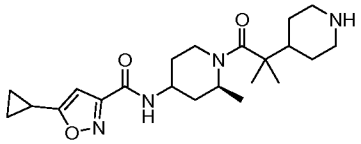
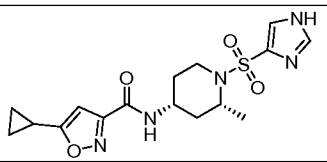
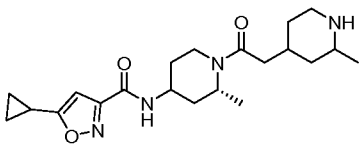
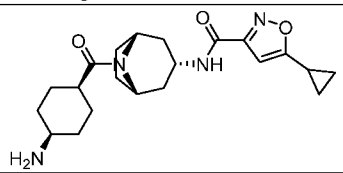
145		HCl	**408**		None
146		TFA	**409**		None
147		TFA	**410**		None

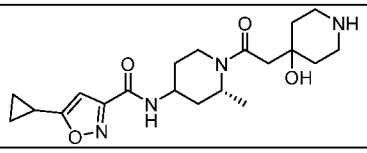
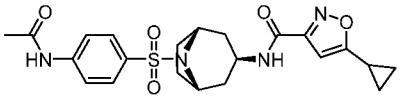
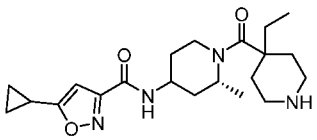
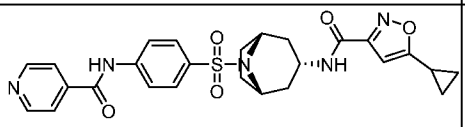
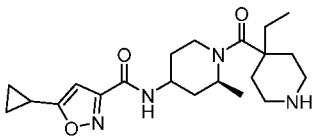
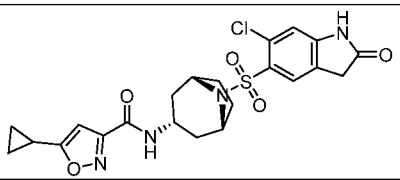
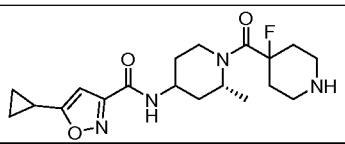
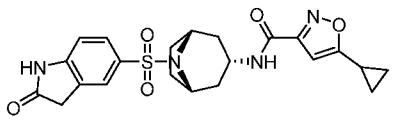
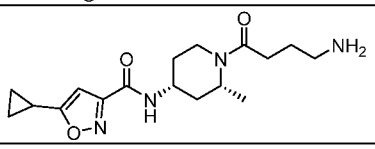
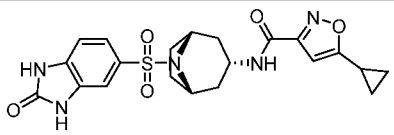
148		TFA	**411**		None
149		TFA	**412**		None
150		None	**413**		None
151		TFA	**414**		None

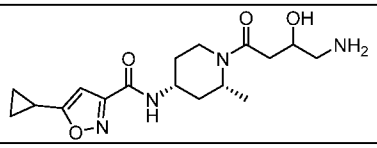
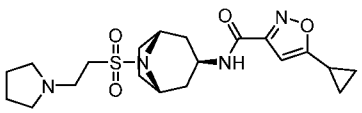
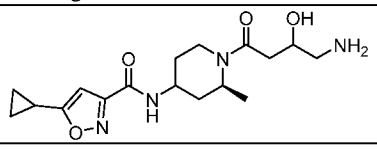
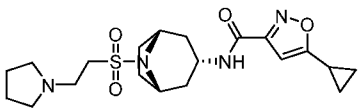
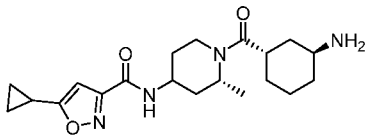
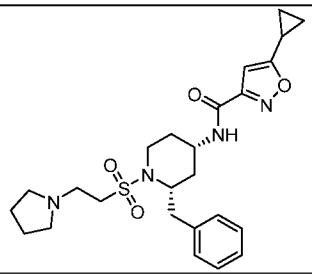
152		TFA	**415**		None
153		TFA	**416**		None
154		TFA	**417**		None
155		TFA	**418**		None

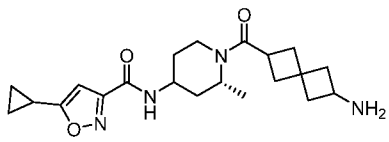
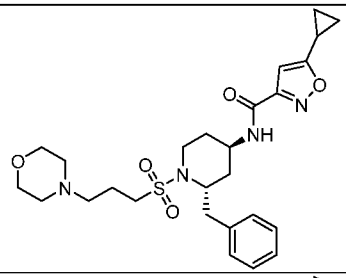
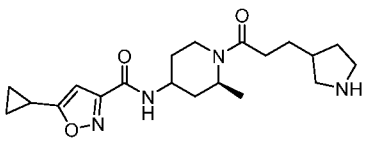
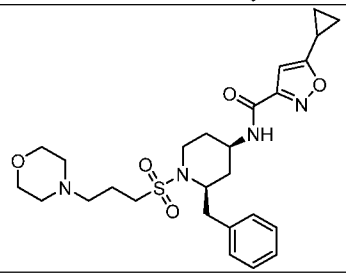
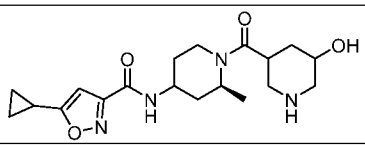
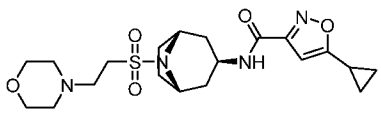
156		TFA	**419**		None
157		TFA	**420**		None
158		TFA	**421**		HCl
159		TFA	**422**		HCl

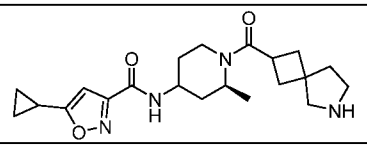
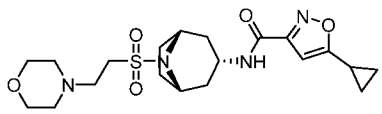
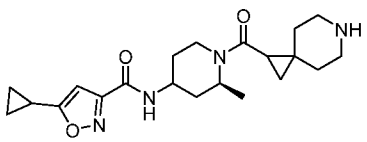
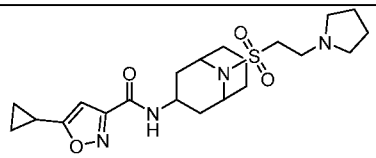
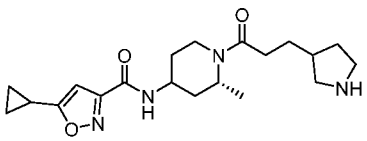
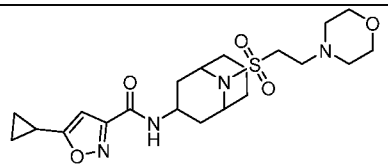
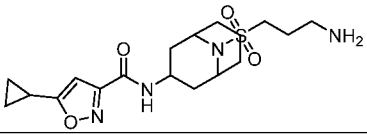
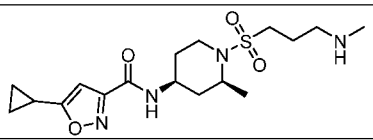
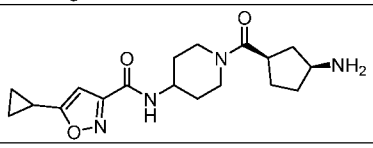
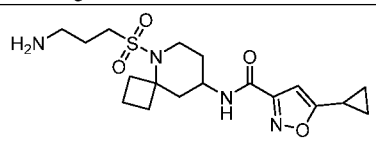
160		TFA	**423**		HCl
161		TFA	**424**		HCl
162		HCl	**425**		HCl

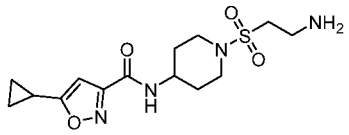
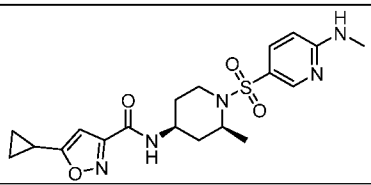
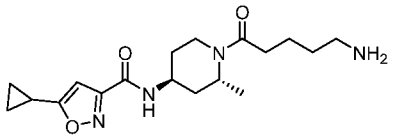
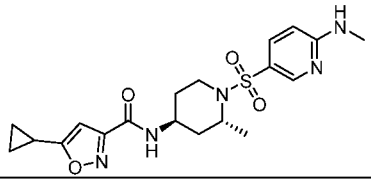
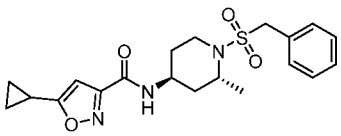
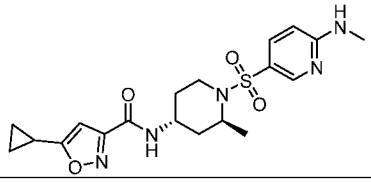
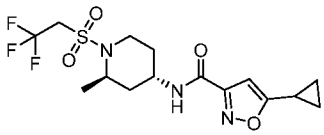
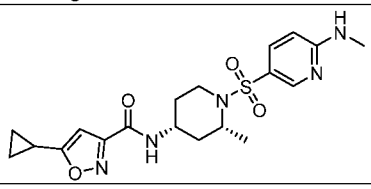
163		HCl	**426**		None
164		HCl	**427**		None
165		HCl	**428**		None
166		HCl	**429**		None

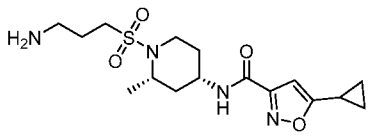
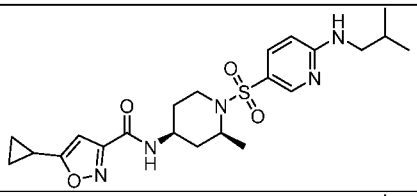
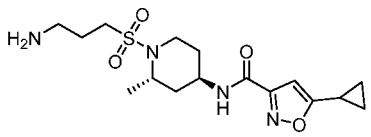
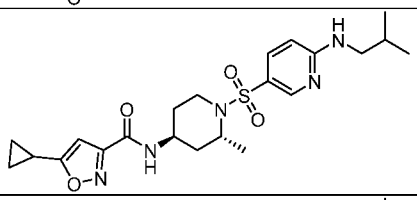
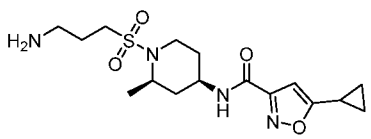
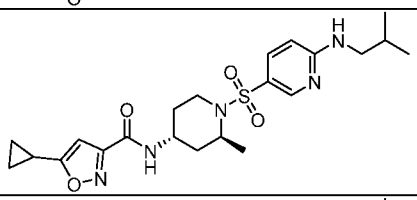
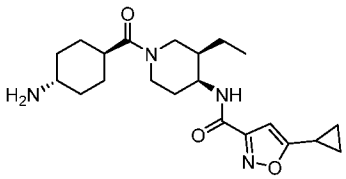
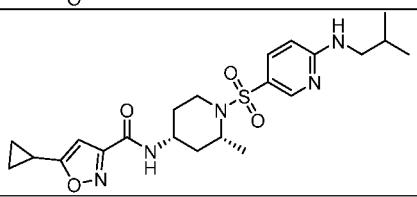
167		HCl	**430**		None
168		HCl	**431**		None
169		HCl	**432**		None
170		HCl	**433**		None
171		HCl	**434**		None

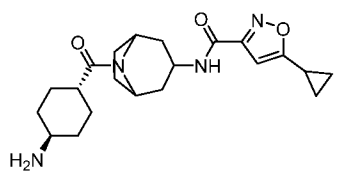
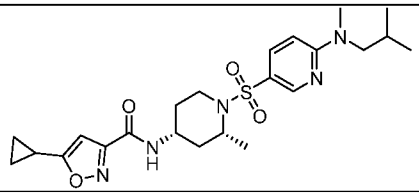
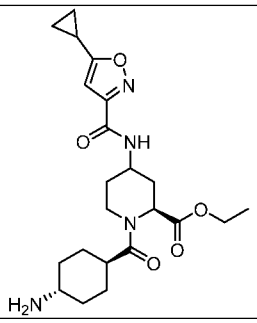
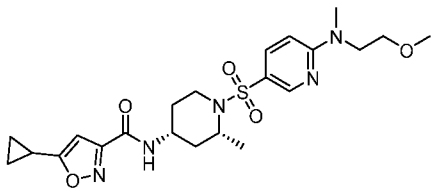
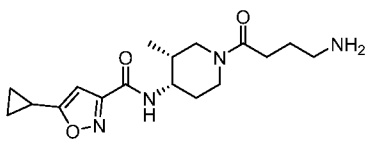
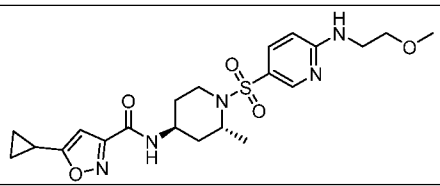
172		HCl	**435**		None
173		HCl	**436**		None
174		HCl	**437**		HCl

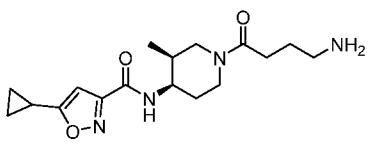
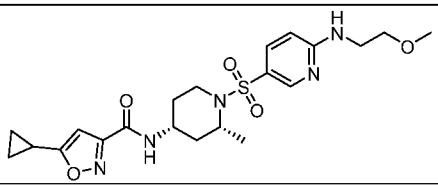
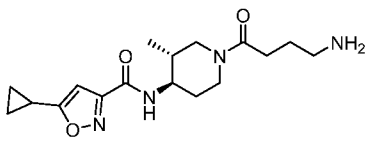
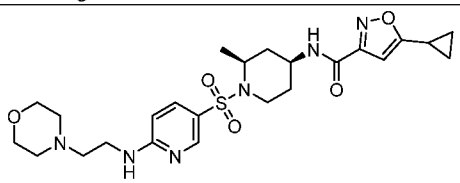
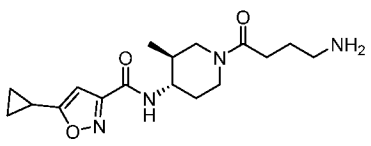
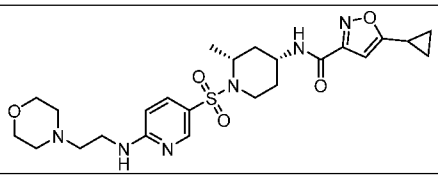
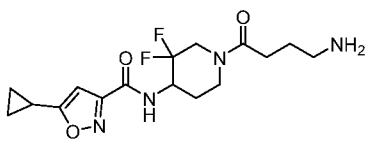
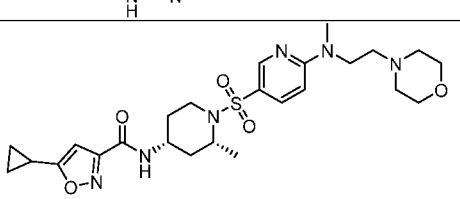
175		HCl	**438**		TFA
176		HCl	**439**		TFA
177		HCl	**440**		None

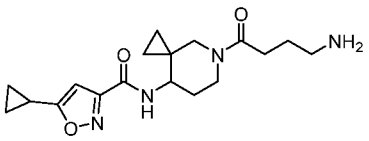
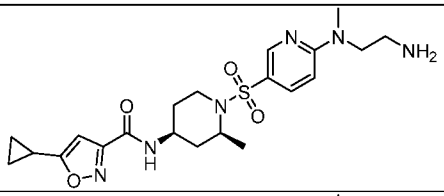
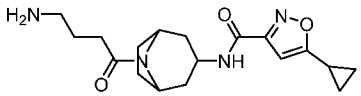
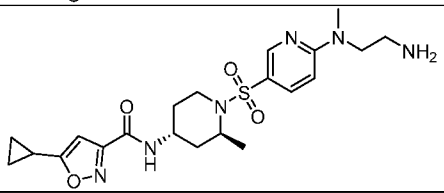
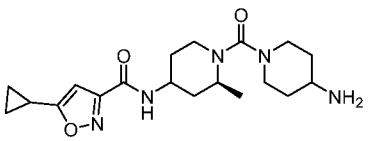
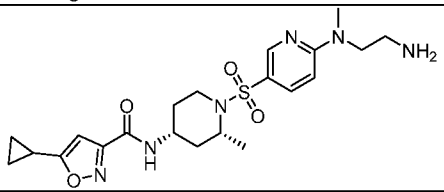
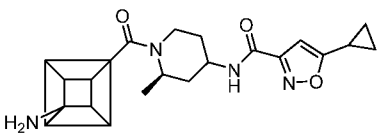
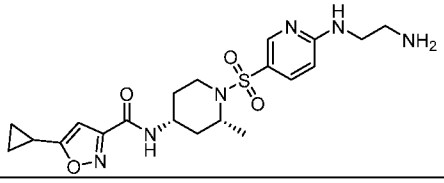
178		TFA	**441**		None
179		TFA	**442**		None
180		HCl	**443**		None
181		HCl	**444**		None
182		TFA	**445**		HCl

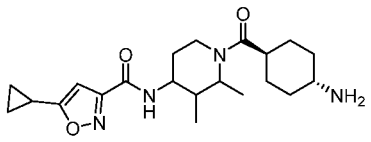
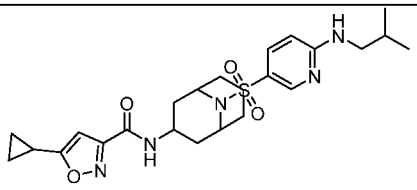
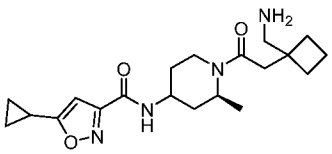
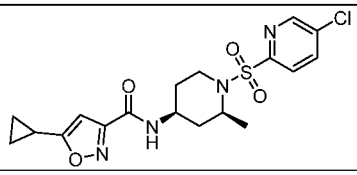
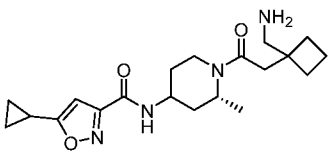
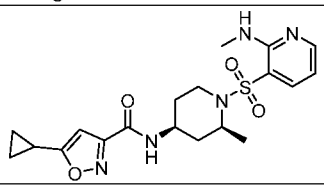
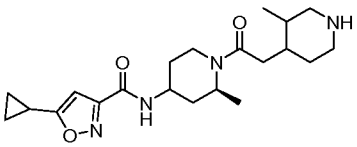
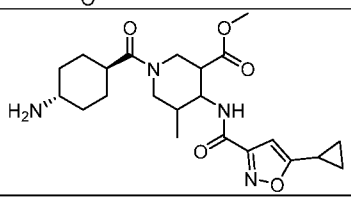
183		HCl	**446**		None
184		HCl	**447**		None
185		None	**448**		None
186		None	**449**		None

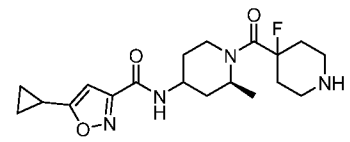
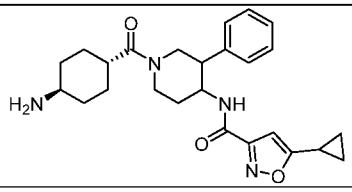
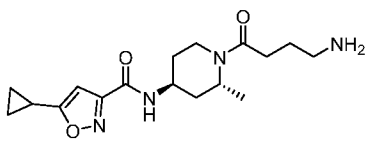
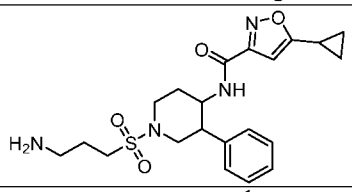
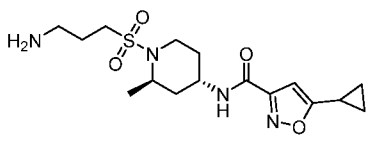
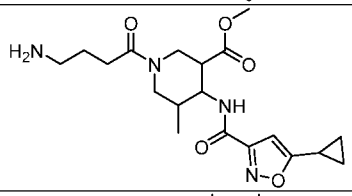
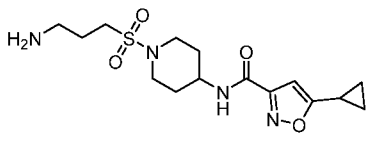
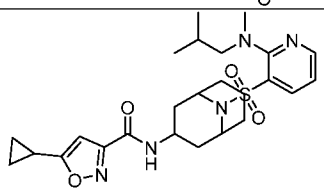
187		HCl	**450**		None
188		HCl	**451**		None
189		HCl	**452**		None
190		HCl	**453**		None

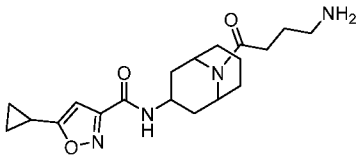
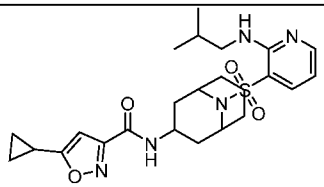
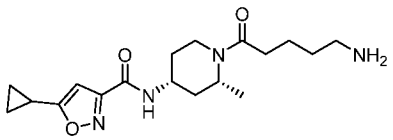
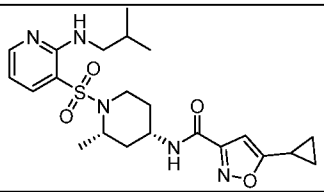
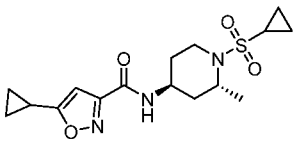
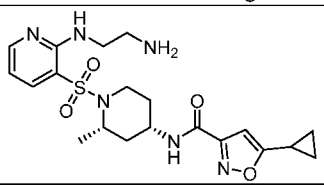
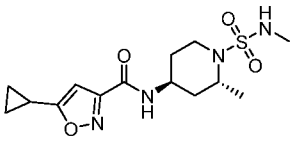
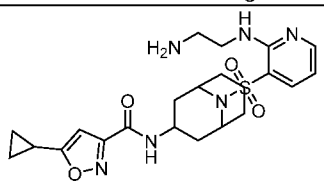
191		TFA	**454**		None
192		TFA	**455**		None
193		TFA	**456**		None

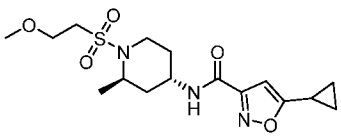
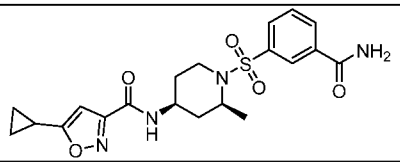
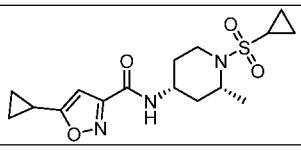
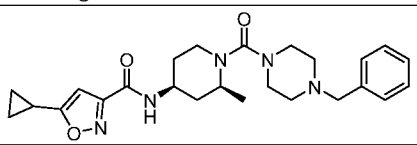
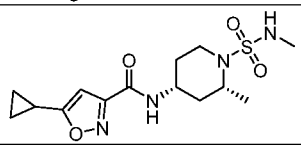
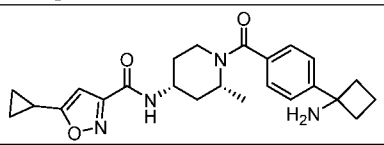
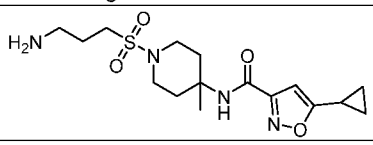
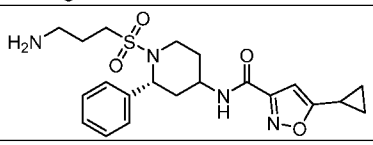
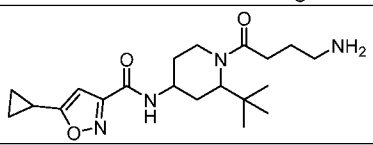
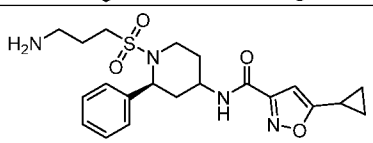
194		TFA	**457**		None
195		TFA	**458**		None
196		TFA	**459**		None
197		TFA	**460**		None

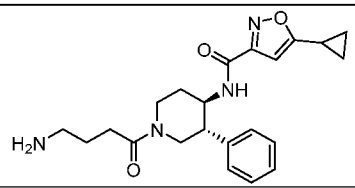
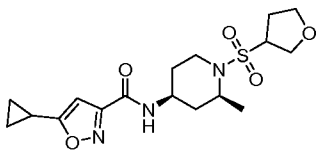
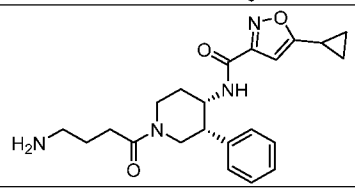
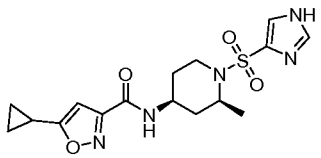
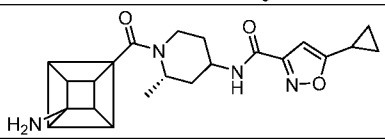
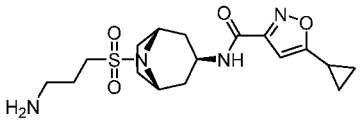
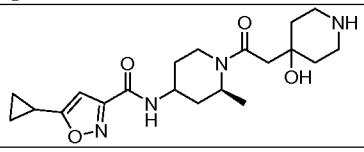
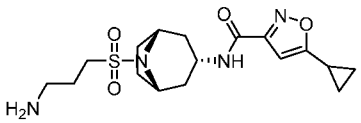
198		TFA	**461**		HCl
199		HCl	**462**		HCl
201		None	**463**		HCl
202		TFA	**464**		None

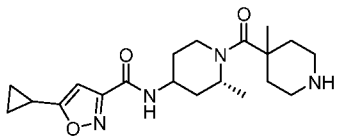
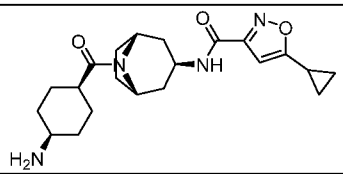
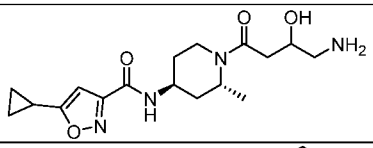
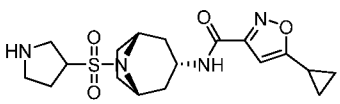
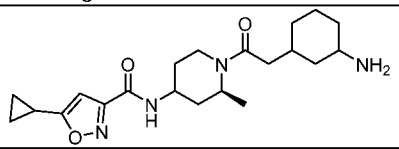
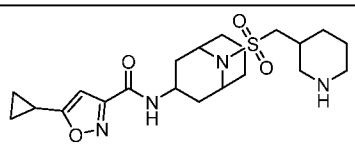
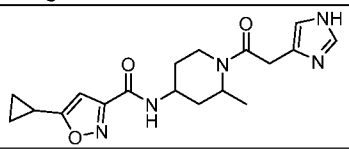
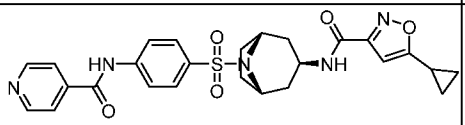
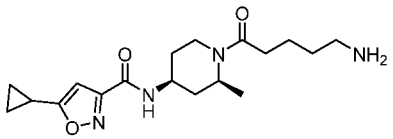
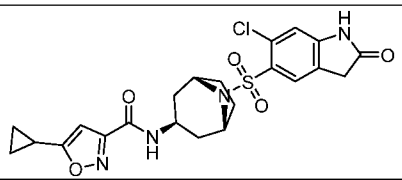
203		None	**465**		None
204		HCl	**466**		None
205		HCl	**467**		None
206		HCl	**468**		TFA

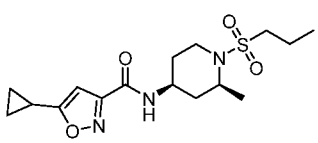
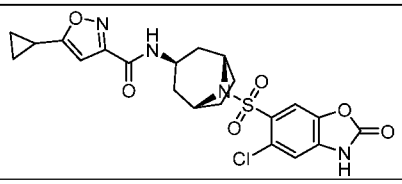
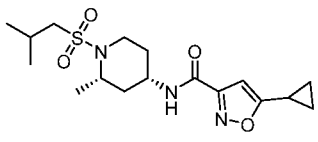
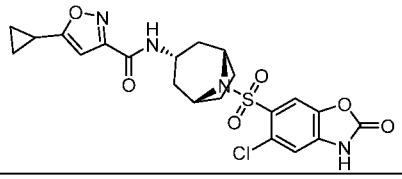
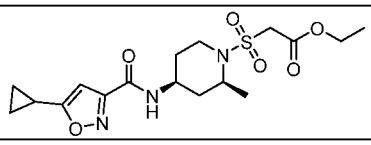
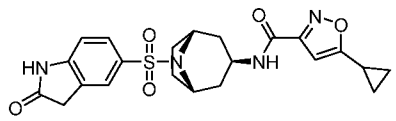
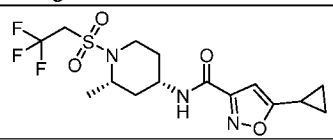
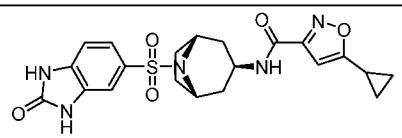
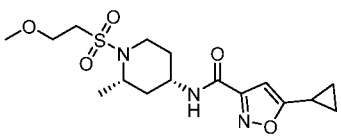
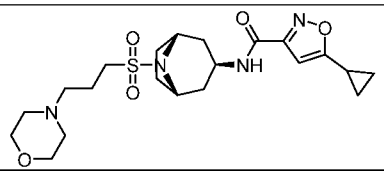
207		HCl	**469**		None
208		HCl	**470**		TFA
209		HCl	**471**		TFA
210		None	**472**		None

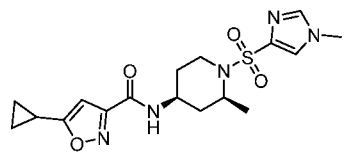
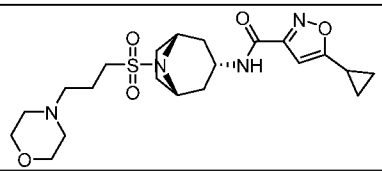
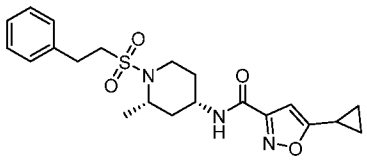
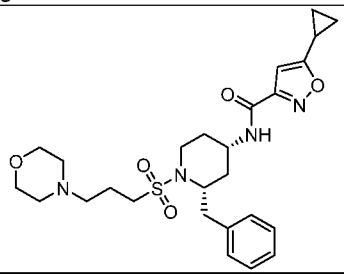
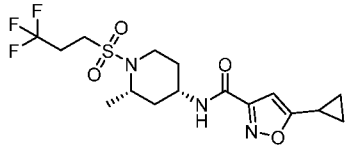
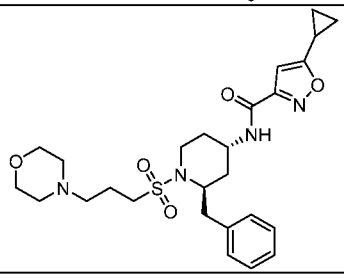
211		HCl	**473**		None
212		HCl	**474**		None
213		None	**475**		None
214		None	**476**		None

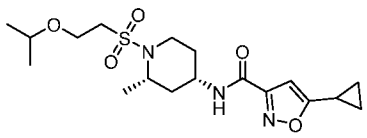
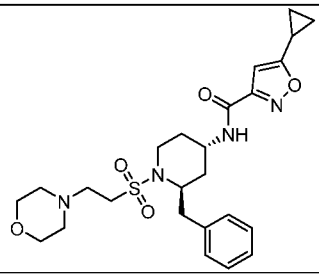
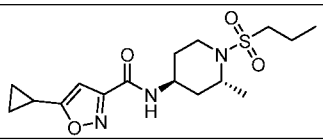
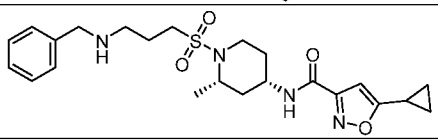
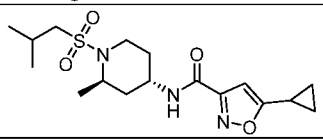
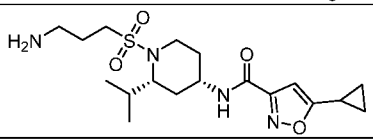
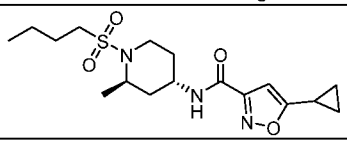
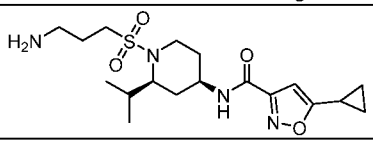
215		None	**477**		None
216		None	**478**		None
217		None	**479**		HCl
218		TFA	**480**		None
219		TFA	**481**		None

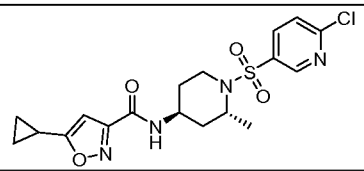
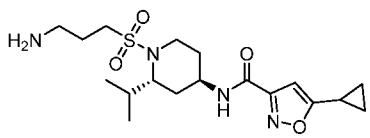
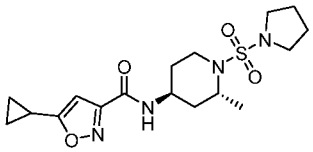
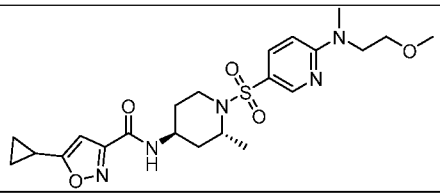
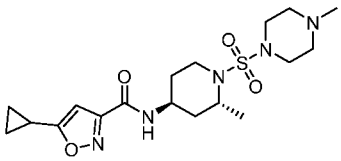
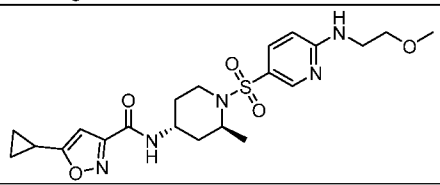
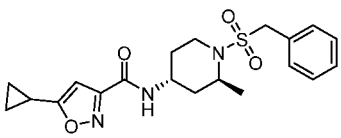
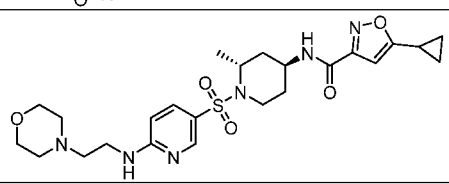
220		TFA	**482**		None
221		TFA	**483**		None
222		TFA	**484**		None
223		None	**485**		None

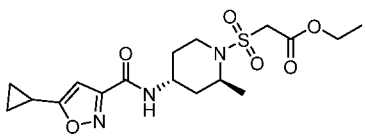
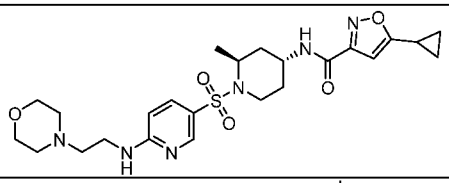
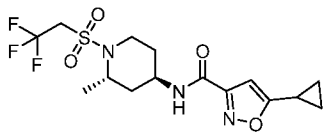
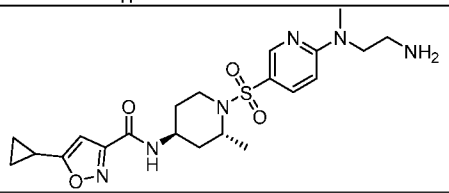
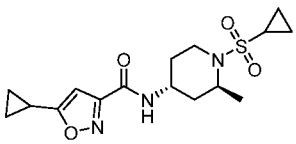
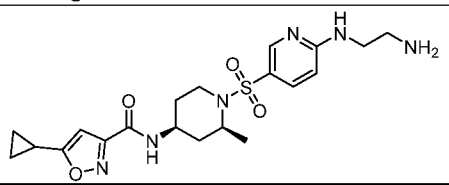
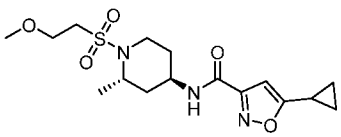
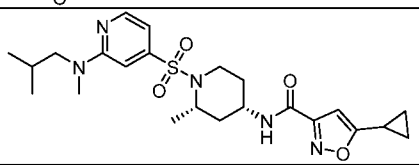
224		HCl	**486**		None
225		HCl	**487**		None
226		HCl	**488**		TFA
227		None	**489**		None
228		HCl	**490**		None

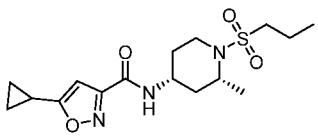
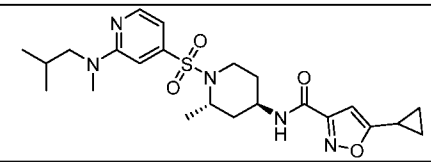
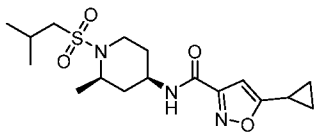
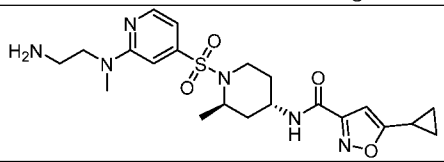
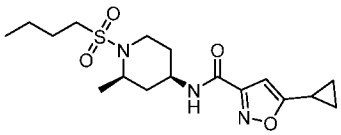
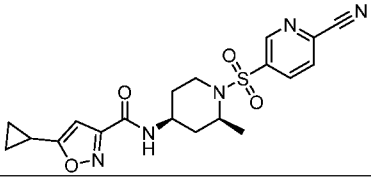
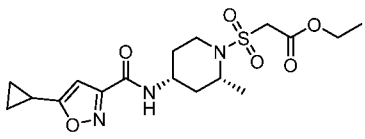
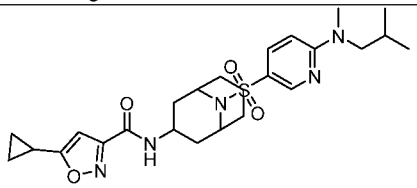
229		None	**491**		None
230		None	**492**		None
231		None	**493**		None
232		None	**494**		None
233		None	**495**		None

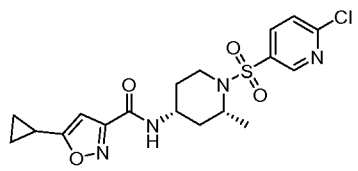
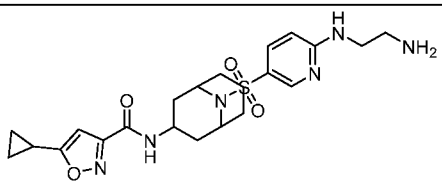
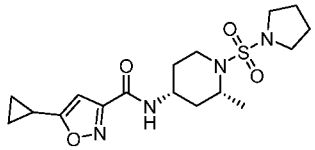
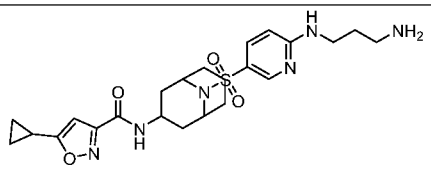
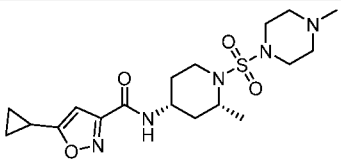
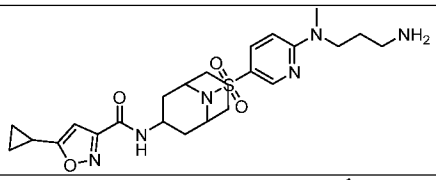
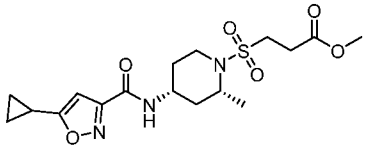
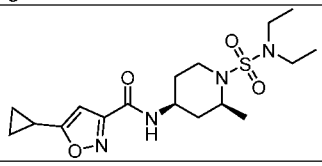
234		HCl	**496**		None
235		HCl	**497**		HCl
236		HCl	**498**		HCl

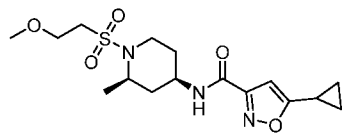
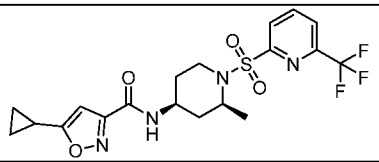
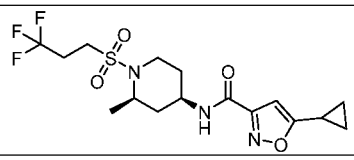
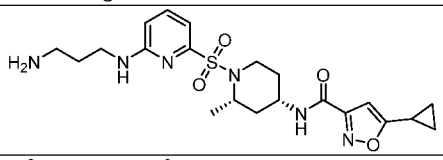
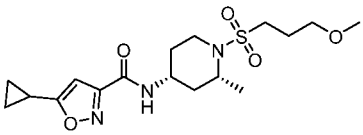
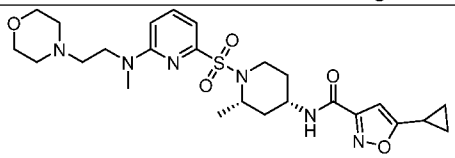
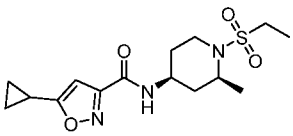
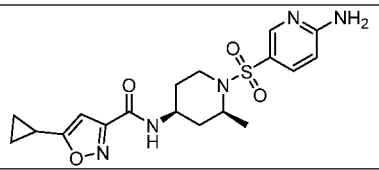
237		HCl	**499**		None
238		None	**500**		None
239		None	**501**		HCl
240		None	**502**		HCl

241		None	**503**		HCl
242		None	**504**		None
243		None	**505**		None
244		None	**506**		HCl

245		None	**507**		HCl
246		None	**508**		HCl
247		None	**509**		None
248		None	**510**		None

249		None	**511**		None
250		None	**512**		HCl
251		None	**513**		None
252		None	**514**		None

253		None	**515**		None
254		None	**516**		None
255		None	**517**		None
256		None	**518**		None

257		None	**519**		None
258		HCl	**520**		HCl
259		HCl	**521**		None
260		None	**522**		HCl

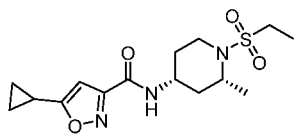
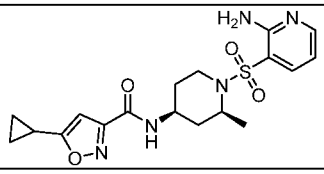
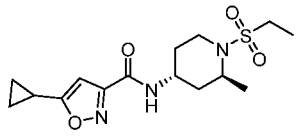
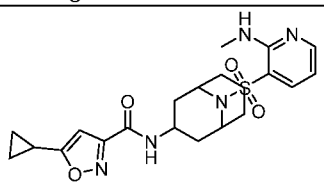
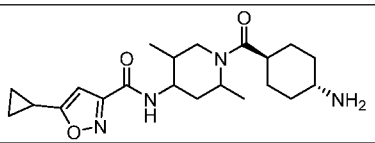
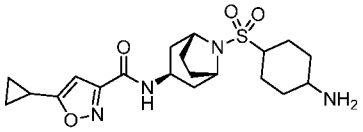
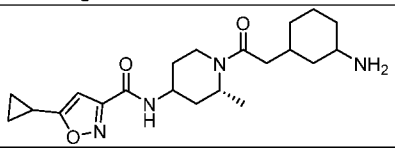
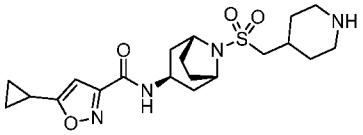
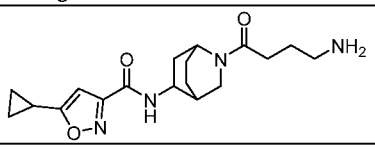
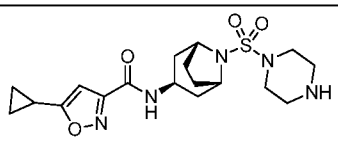
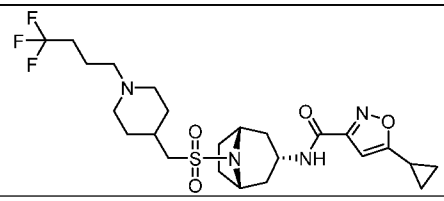
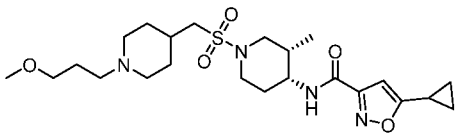
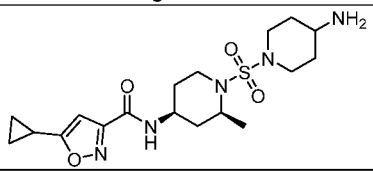
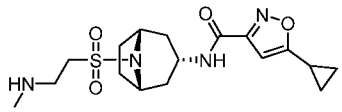
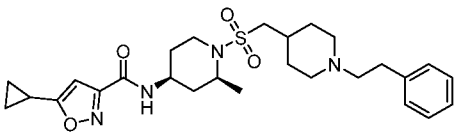
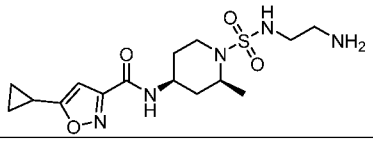
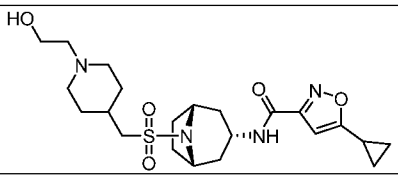
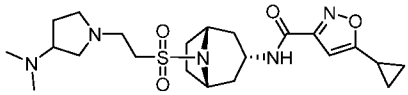
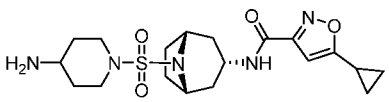
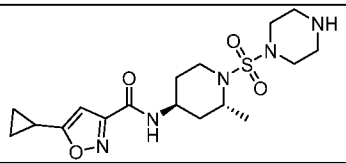
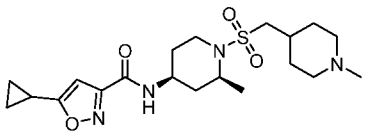
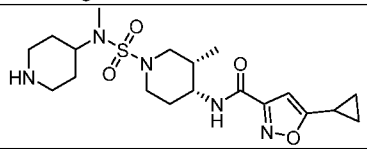
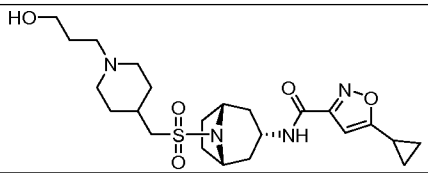
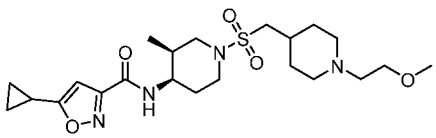
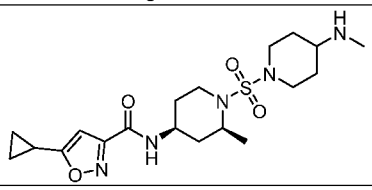
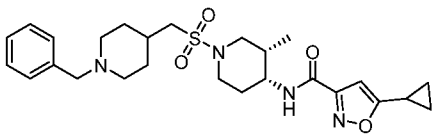
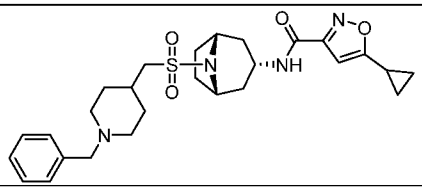
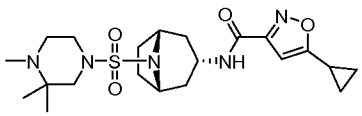
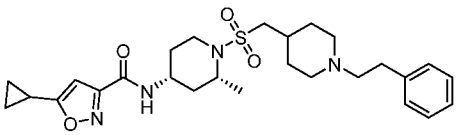
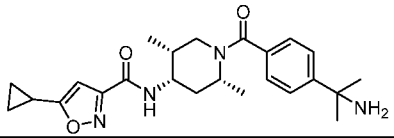
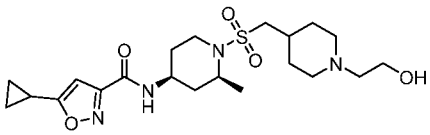
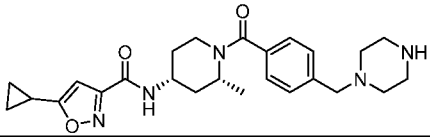
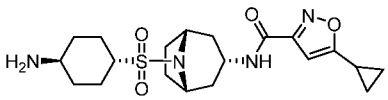
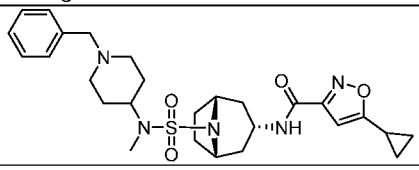
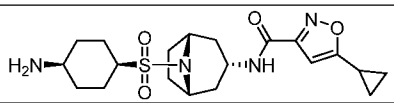
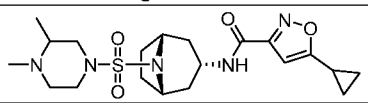
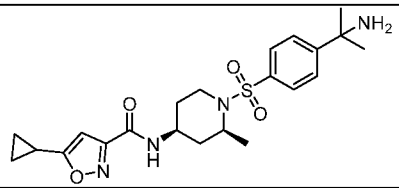
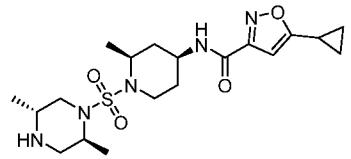
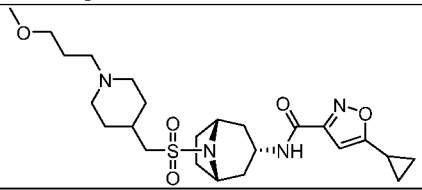
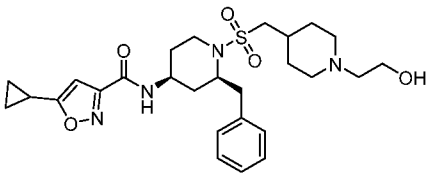
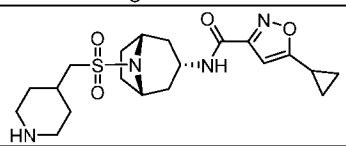
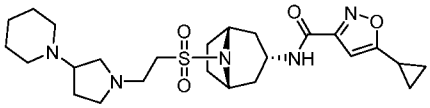
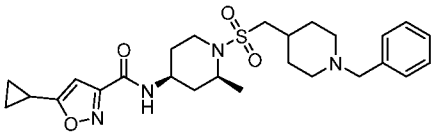
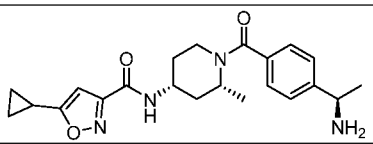
261		None	**523**		HCl
262		None	**524**		None
263		None	**525**		None
264		HCl	**526**		None
265		HCl	**527**		HCl

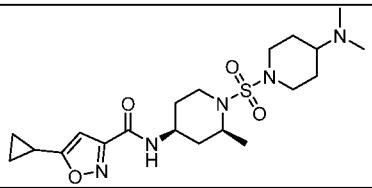
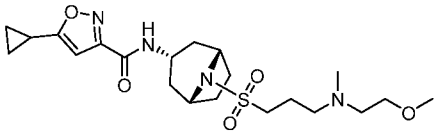
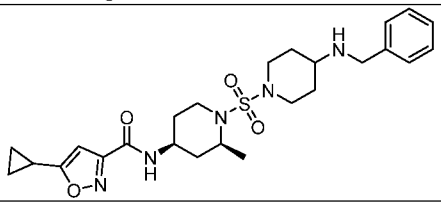
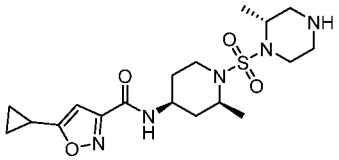
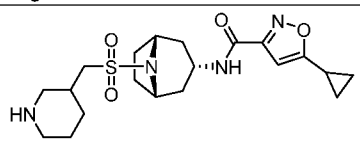
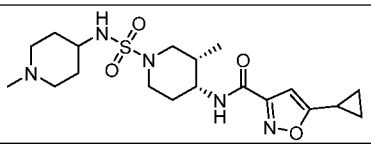
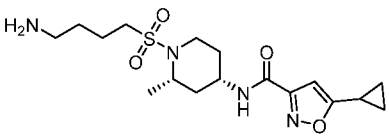
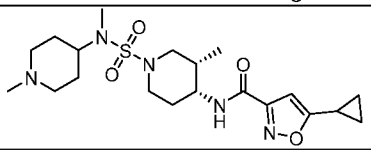
Table 2

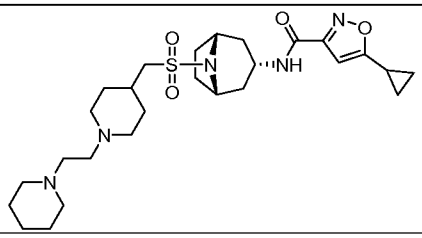
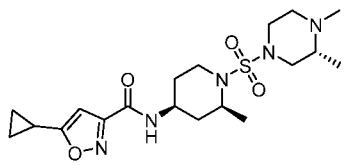
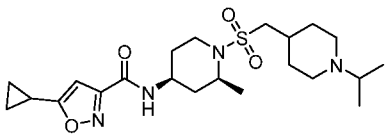
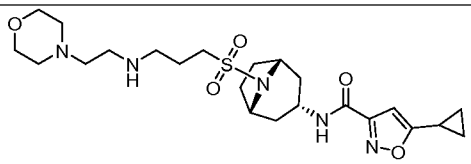
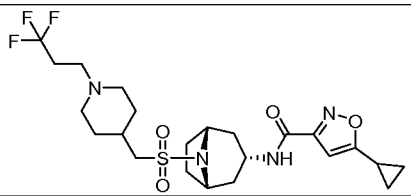
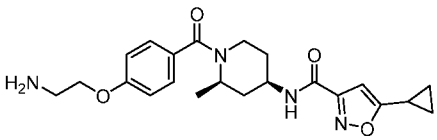
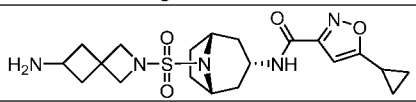
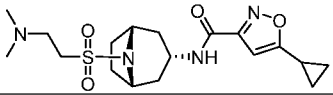
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
528		None	**648**		None
529		TFA	**649**		None
530		None	**650**		TFA
531		None	**651**		None

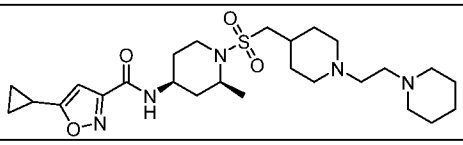
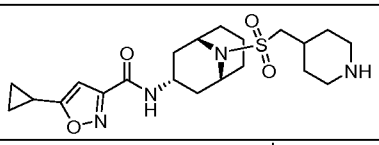
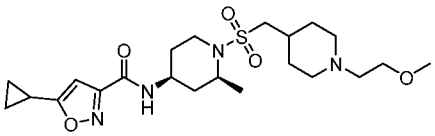
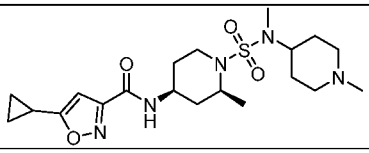
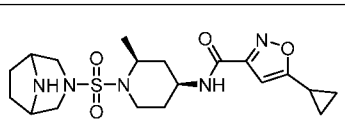
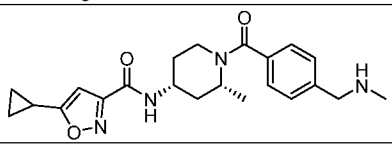
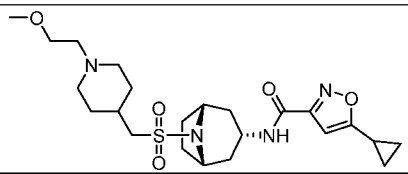
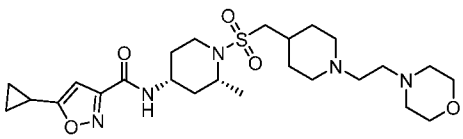
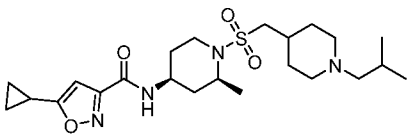
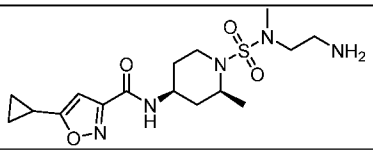
532		TFA	**652**		HCl
533		None	**653**		HCl
534		None	**654**		None
535		None	**655**		HCl

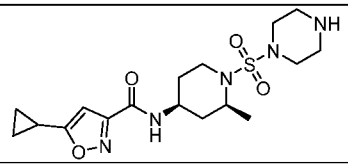
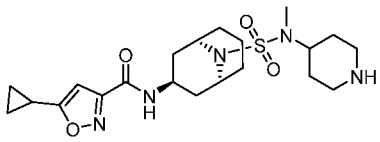
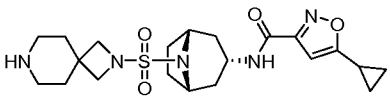
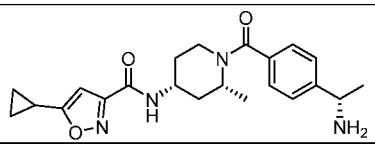
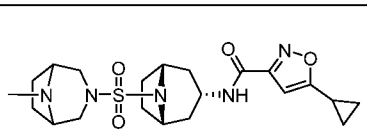
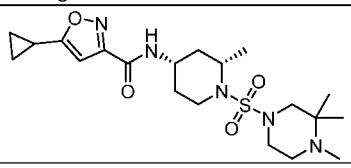
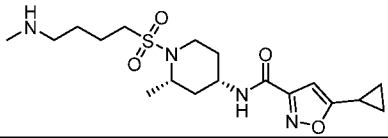
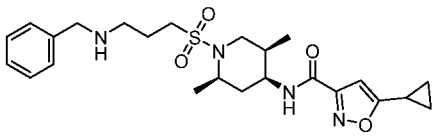
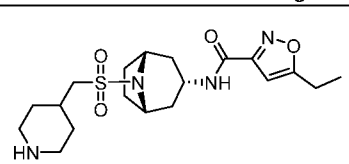
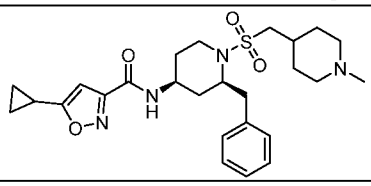
536		HCl	**656**		HCl
537		None	**657**		None
538		None	**658**		None
539		None	**659**		None
540		None	**660**		HCl

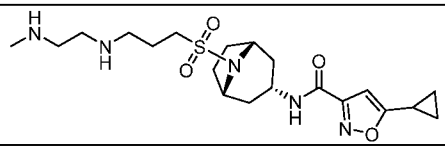
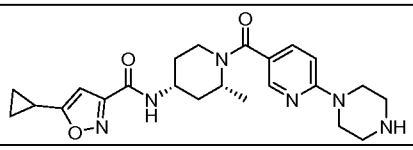
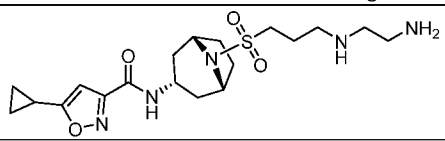
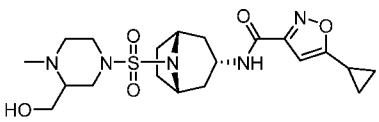
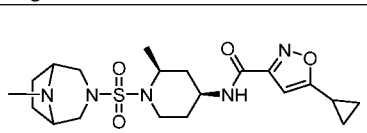
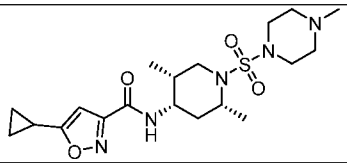
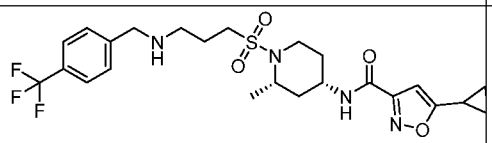
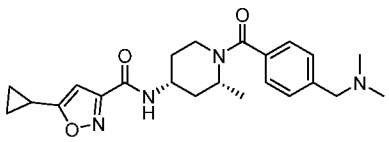
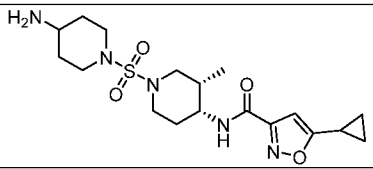
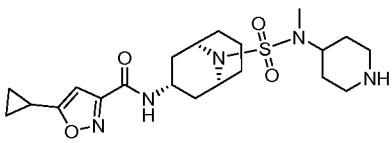
541		None	**661**		None
542		None	**662**		None
543		None	**663**		None
544		None	**664**		None

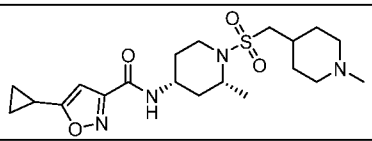
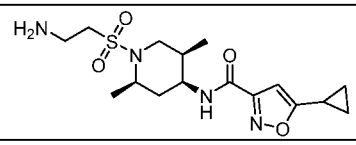
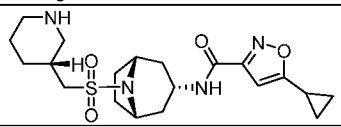
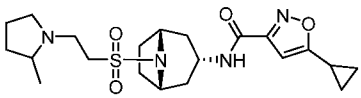
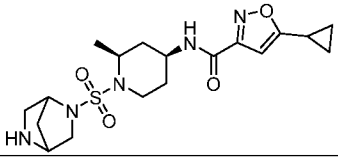
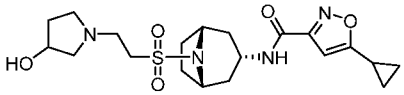
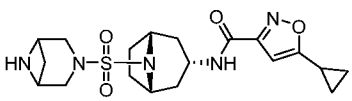
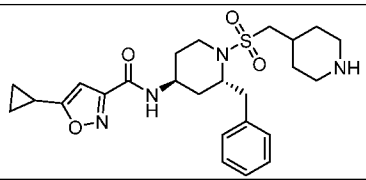
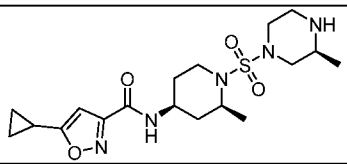
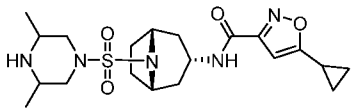
545		TFA	**665**		HCl
546		None	**666**		None
547		None	**667**		HCl
548		None	**668**		HCl

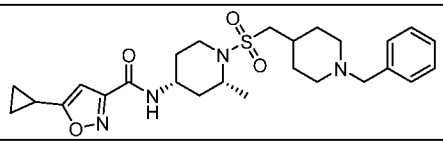
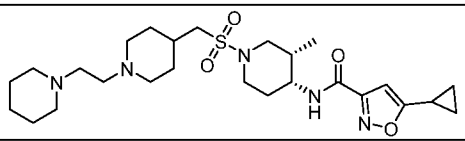
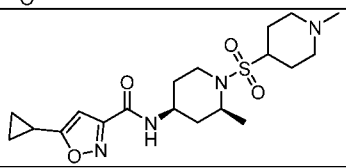
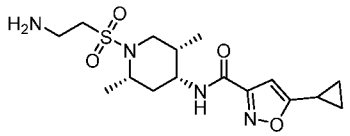
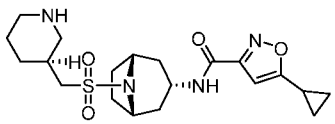
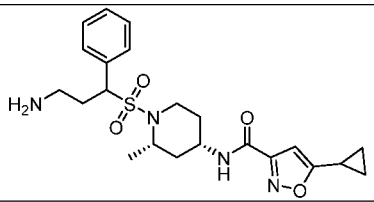
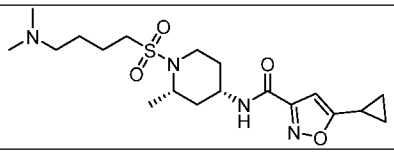
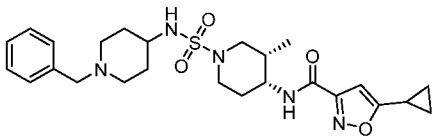
549		HCl	**669**		None
550		None	**670**		HCl
551		None	**671**		None
552		TFA	**672**		None

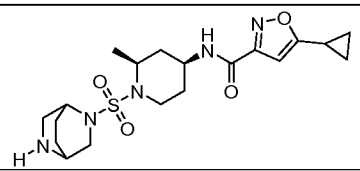
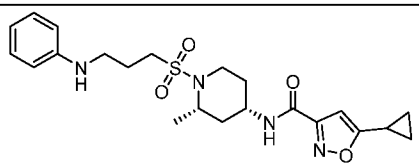
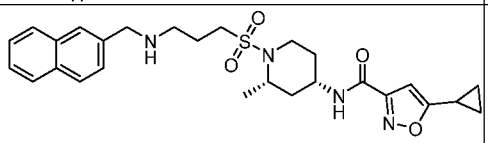
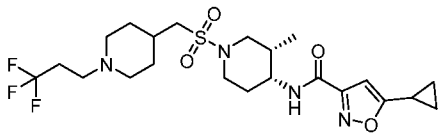
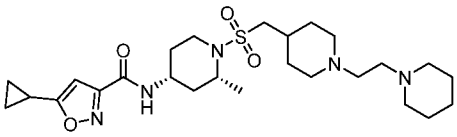
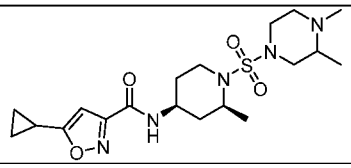
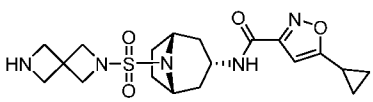
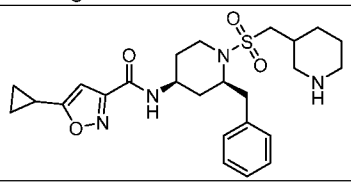
553		None	**673**		HCl
554		None	**674**		HCl
555		None	**675**		None
556		HCl	**676**		None
557		None	**677**		TFA

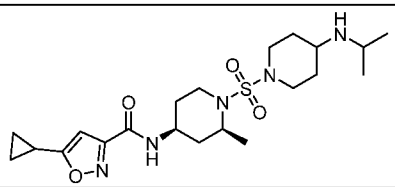
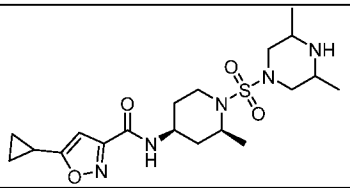
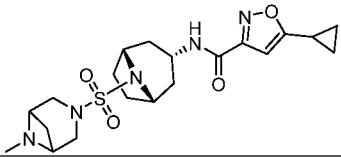
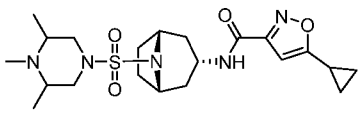
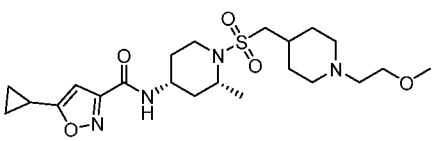
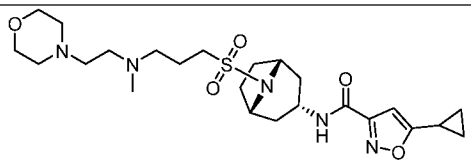
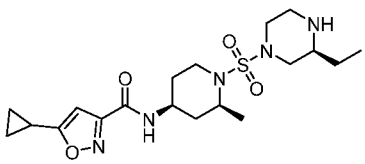
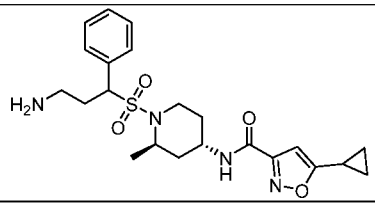
558		HCl	**678**		HCl
559		TFA	**679**		None
560		HCl	**680**		None
561		None	**681**		TFA
562		None	**682**		TFA

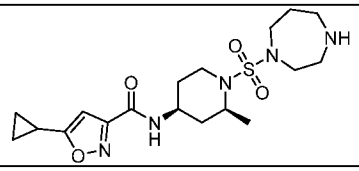
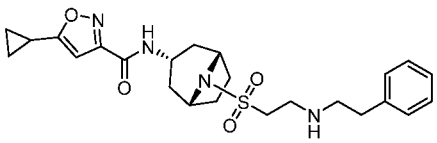
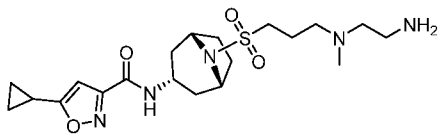
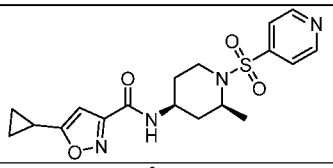
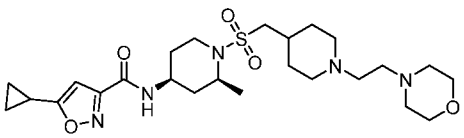
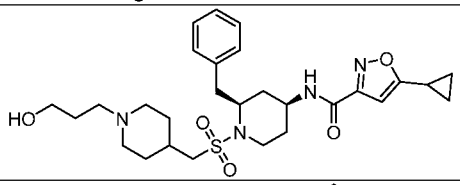
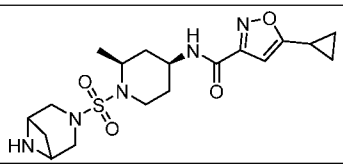
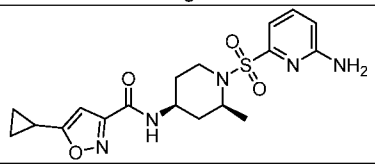
563		HCl	**683**		HCl
564		TFA	**684**		None
565		None	**685**		None
566		None	**686**		None
567		TFA	**687**		HCl

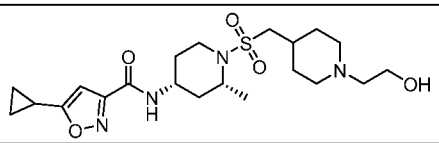
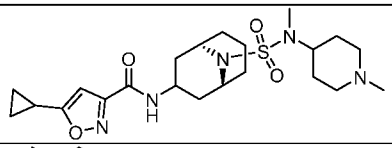
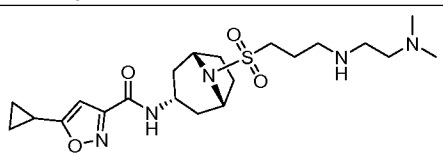
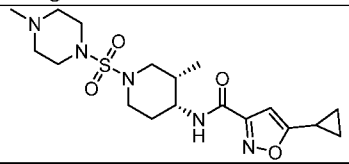
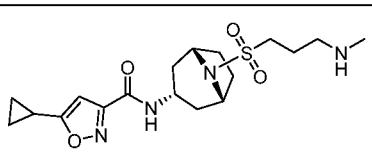
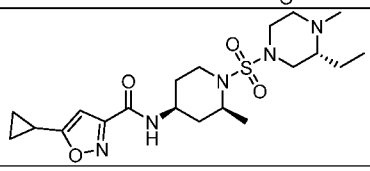
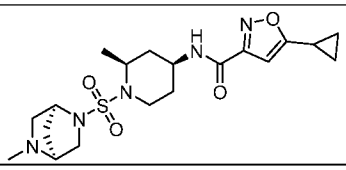
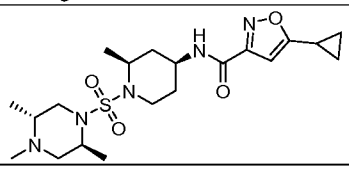
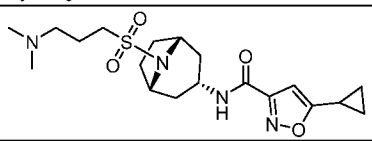
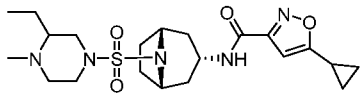
568		None	**688**		None
569		None	**689**		None
570		None	**690**		None
571		HCl	**691**		TFA
572		None	**692**		HCl

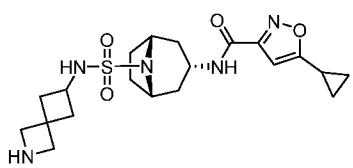
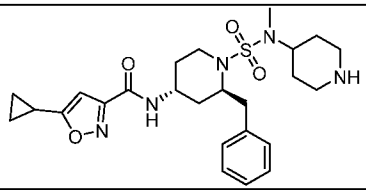
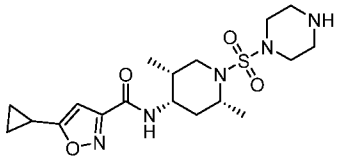
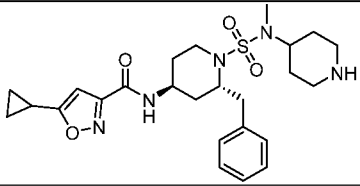
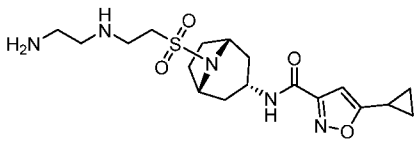
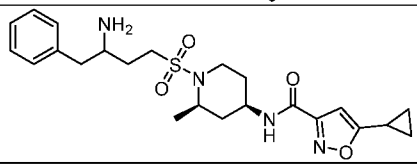
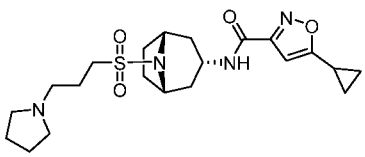
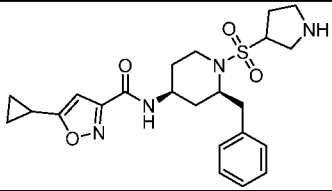
573		None	**693**		None
574		None	**694**		None
575		None	**695**		TFA
576		None	**696**		HCl

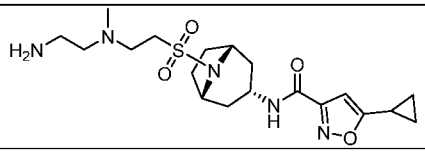
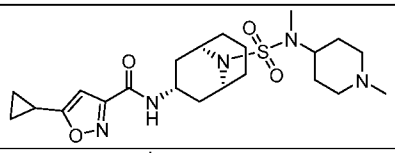
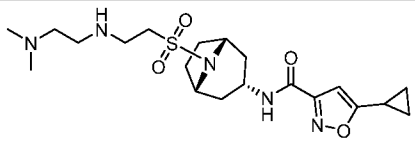
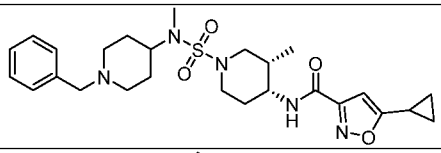
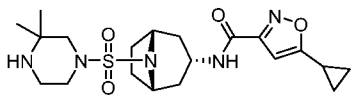
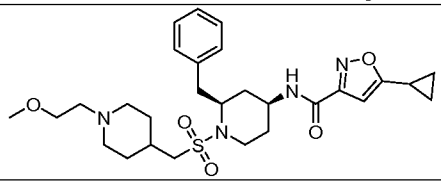
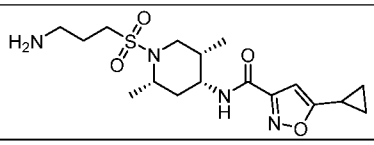
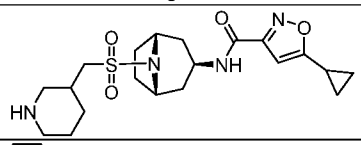
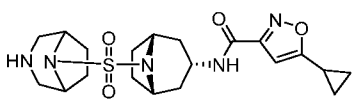
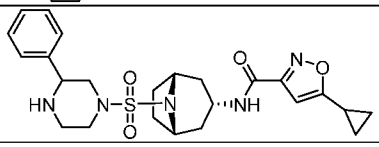
577		None	**697**		None
578		None	**698**		HCl
579		None	**699**		None
580		TFA	**700**		None

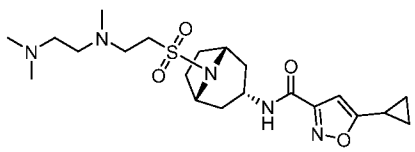
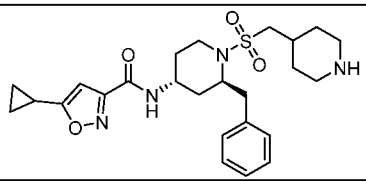
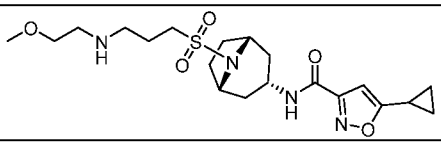
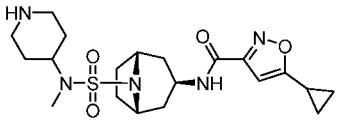
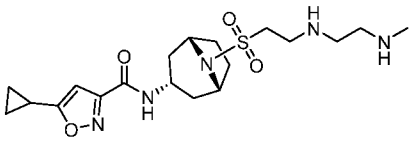
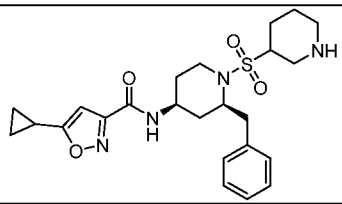
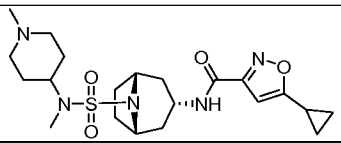
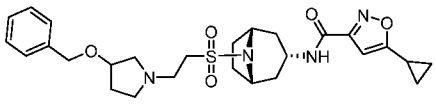
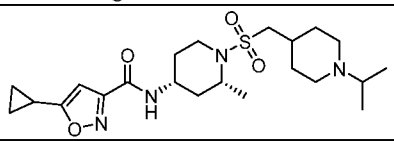
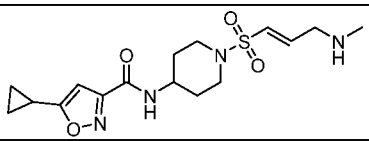
581		HCl	**701**		HCl
582		HCl	**702**		HCl
583		None	**703**		None
584		None	**704**		TFA

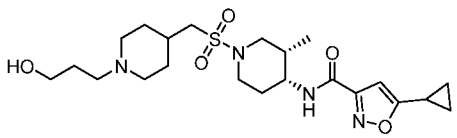
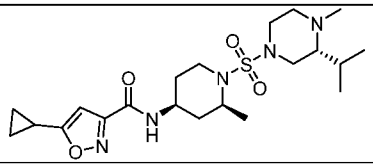
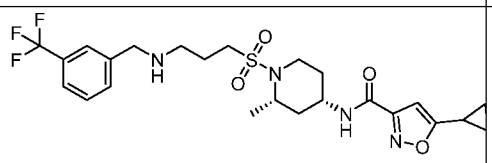
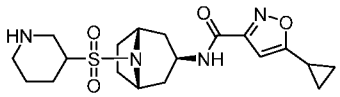
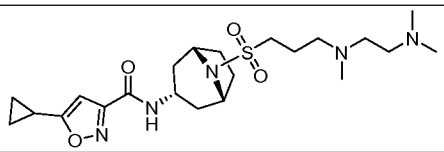
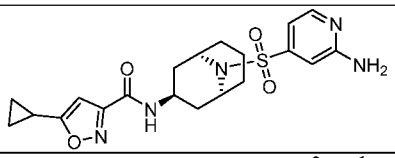
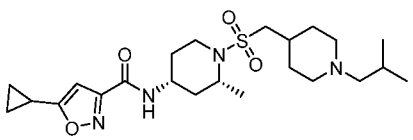
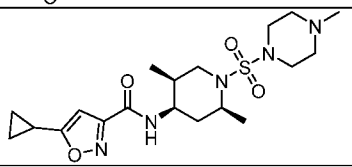
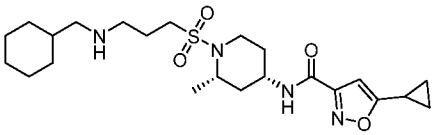
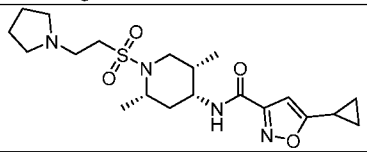
585		None	**705**		None
586		HCl	**706**		None
587		None	**707**		None
588		None	**708**		None

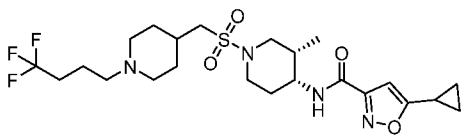
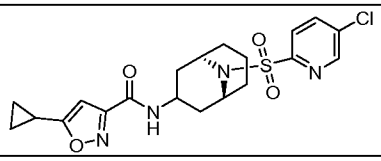
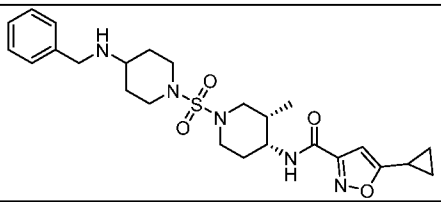
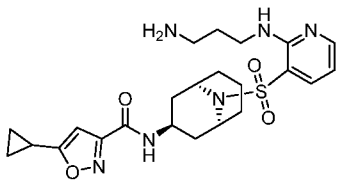
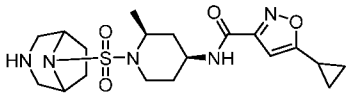
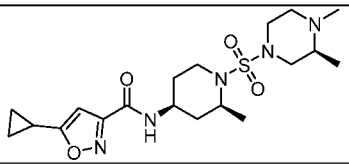
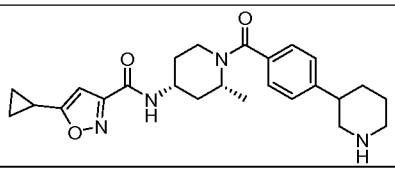
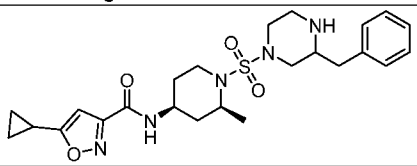
589		None	**709**		None
590		None	**710**		None
591		None	**711**		None
592		None	**712**		None
593		None	**713**		HCl

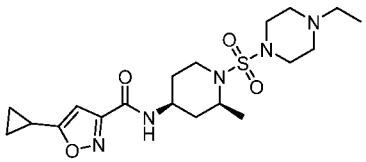
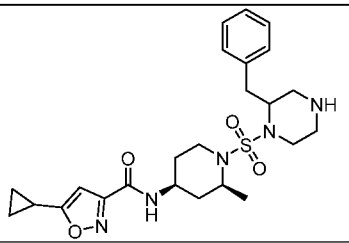
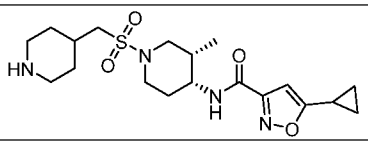
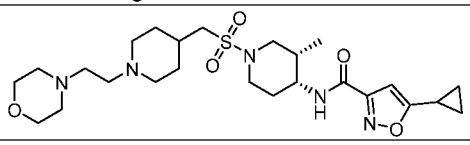
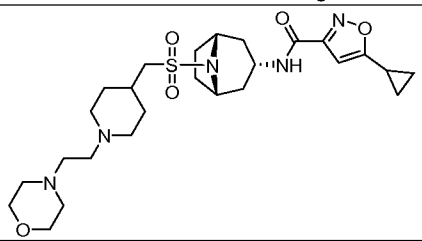
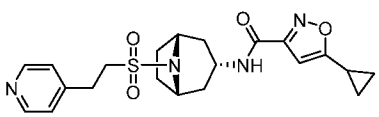
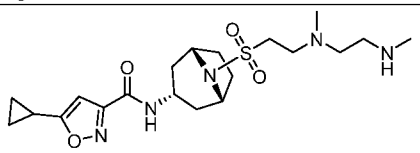
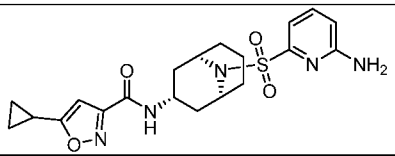
594		TFA	**714**		HCl
595		None	**715**		HCl
596		None	**716**		HCl
597		HCl	**717**		None

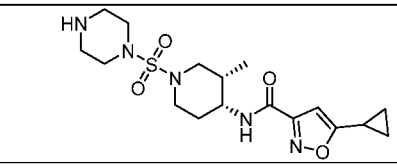
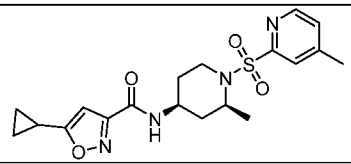
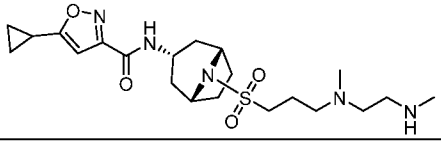
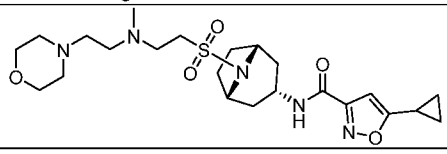
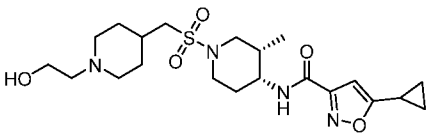
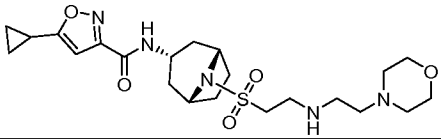
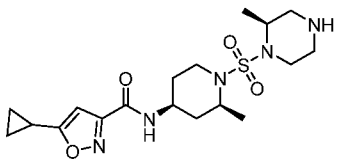
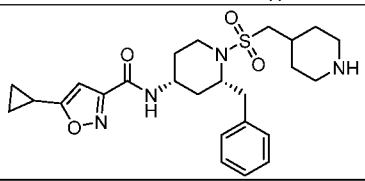
598		TFA	**718**		HCl
599		None	**719**		HCl
600		HCl	**720**		TFA
601		TFA	**721**		None
602		HCl	**722**		TFA

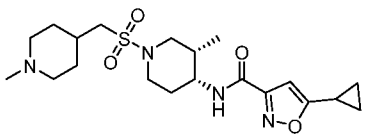
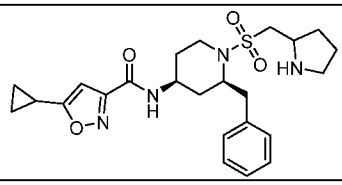
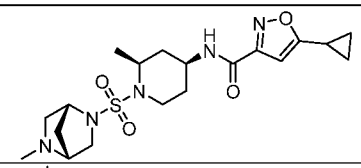
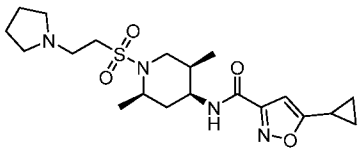
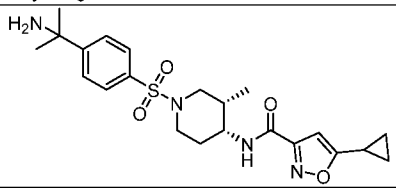
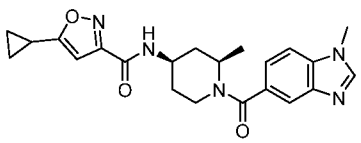
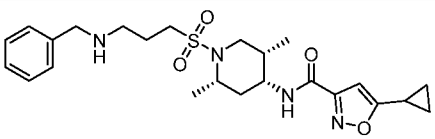
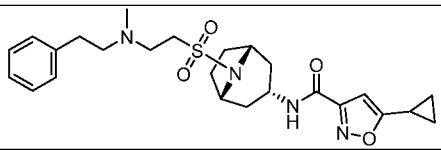
603		TFA	**723**		TFA
604		HCl	**724**		None
605		None	**725**		None
606		None	**726**		None
607		None	**727**		None

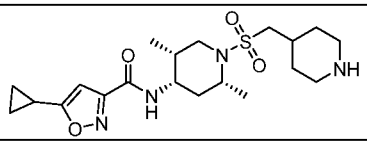
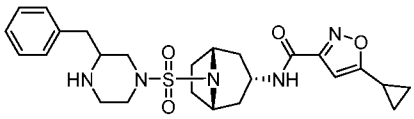
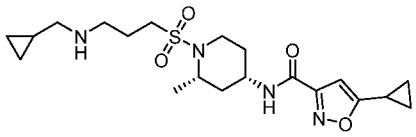
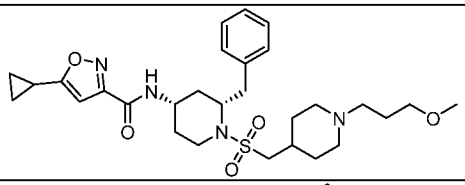
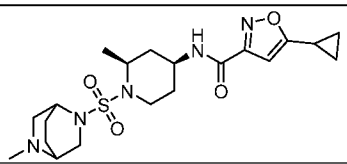
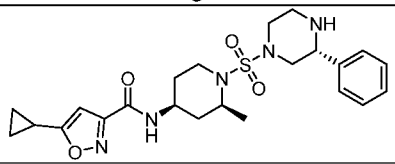
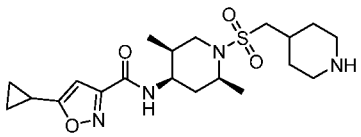
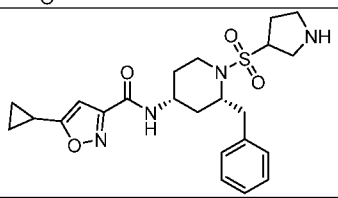
608		None	**728**		None
609		None	**729**		None
610		TFA	**730**		HCl
611		None	**731**		None
612		None	**732**		None

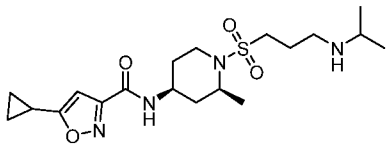
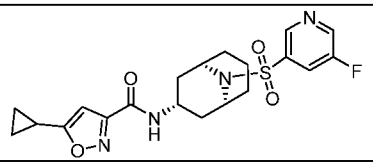
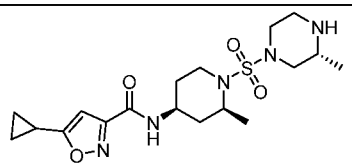
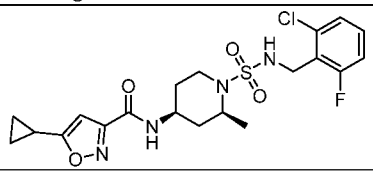
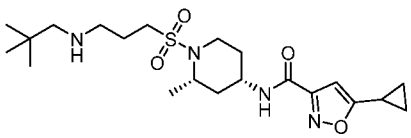
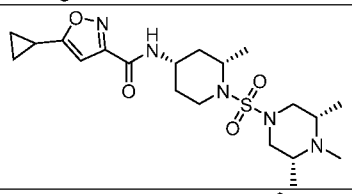
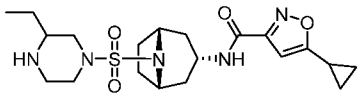
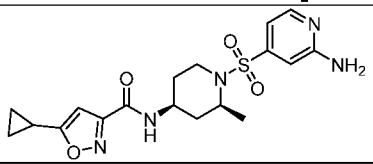
613		HCl	**733**		None
614		None	**734**		HCl
615		None	**735**		None
616		HCl	**736**		None

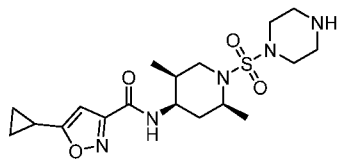
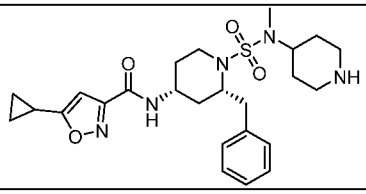
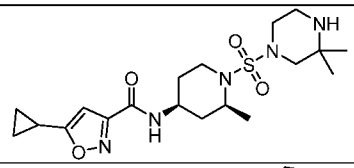
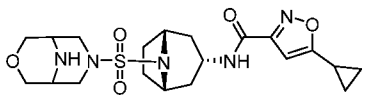
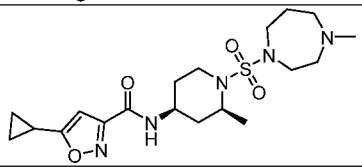
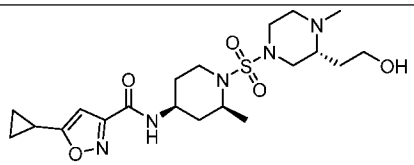
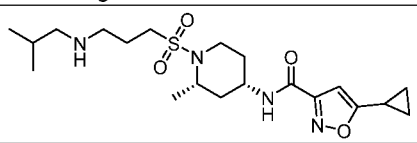
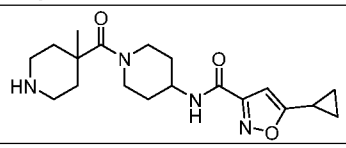
617		HCl	**737**		None
618		HCl	**738**		HCl
619		HCl	**739**		None
620		None	**740**		HCl

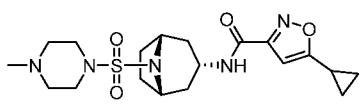
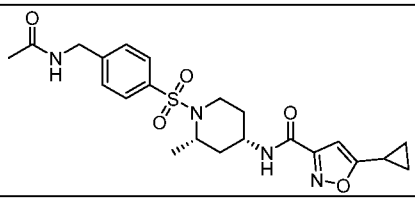
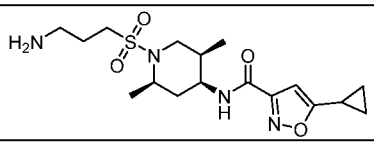
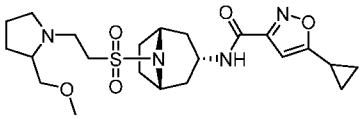
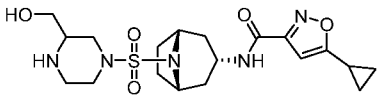
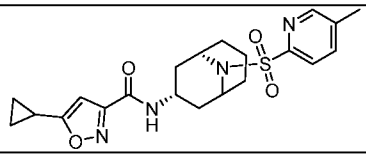
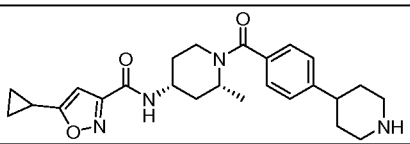
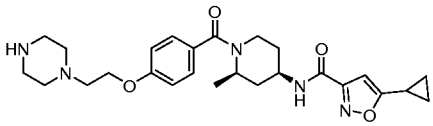
621		HCl	**741**		None
622		HCl	**742**		None
623		None	**743**		None
624		None	**744**		None

625		None	**745**		None
626		None	**746**		None
627		None	**747**		None
628		TFA	**748**		None

629		None	**749**		HCl
630		None	**750**		TFA
631		None	**751**		None
632		None	**752**		None

633		None	**753**		None
634		None	**754**		None
635		None	**755**		None
636		HCl	**756**		HCl

637		None	**757**		HCl
638		HCl	**758**		HCl
639		None	**759**		None
640		None	**760**		TFA

641		HCl	**761**		None
642		None	**762**		None
643		None	**763**		None
644		None	**764**		HCl

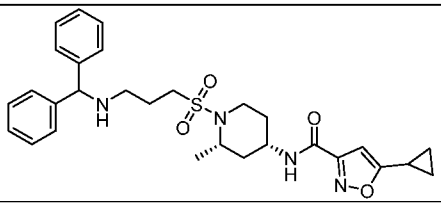
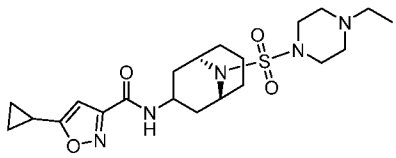
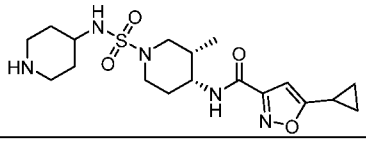
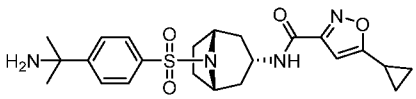
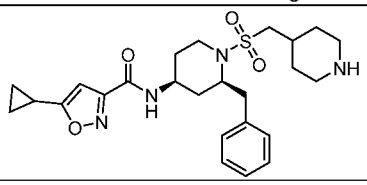
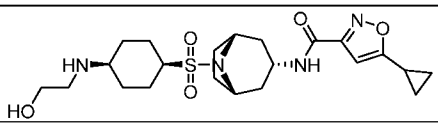
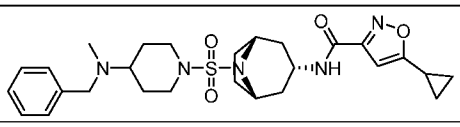
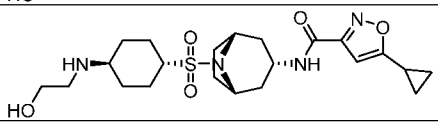
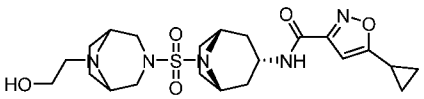
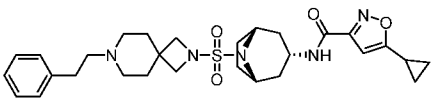
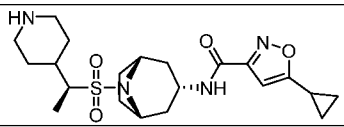
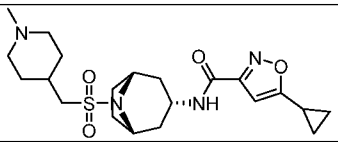
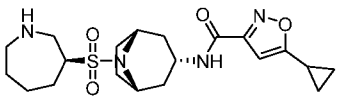
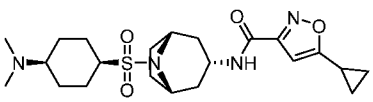
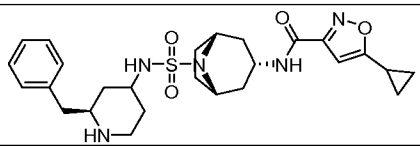
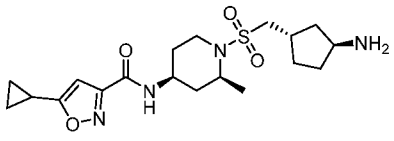
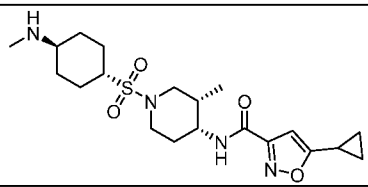
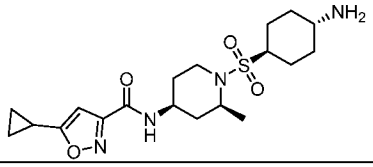
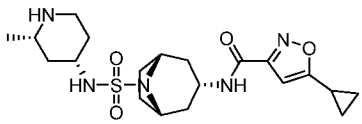
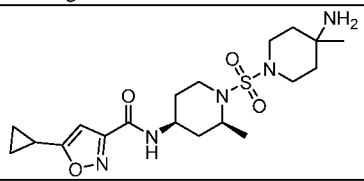
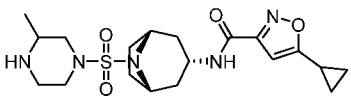
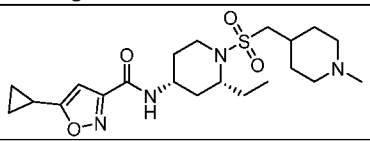
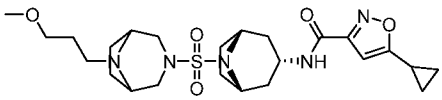
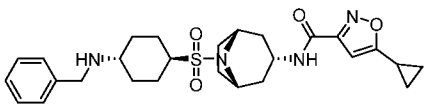
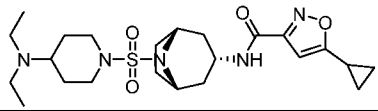
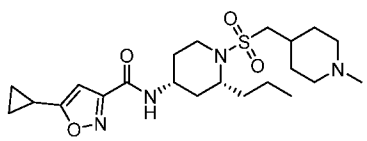
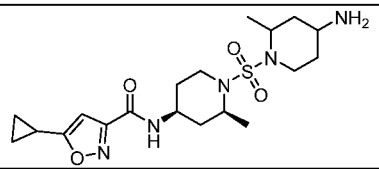
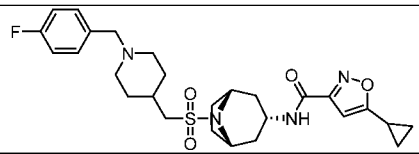
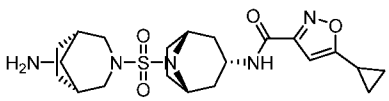
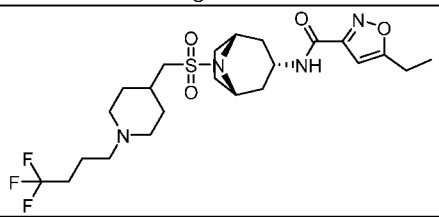
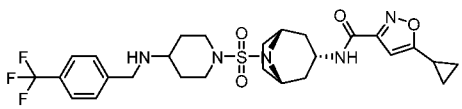
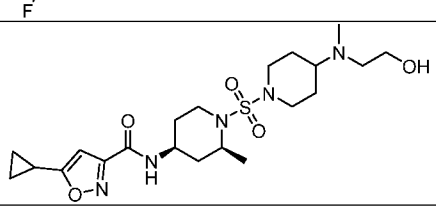
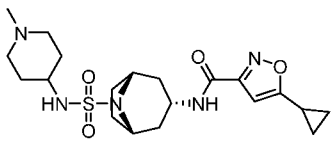
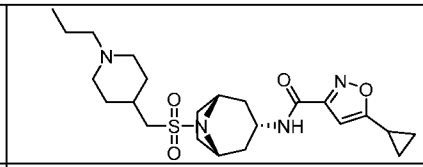
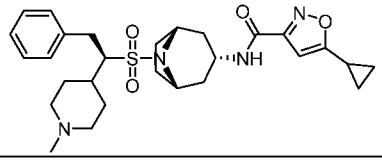
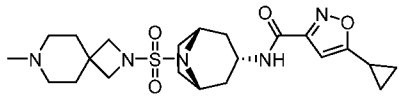
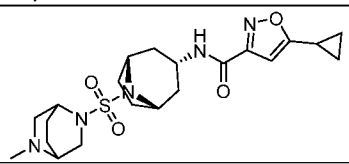
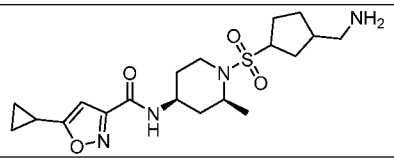
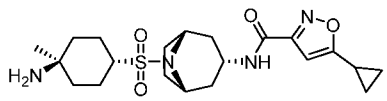
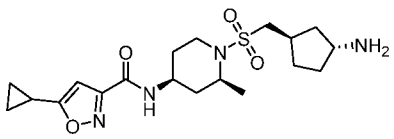
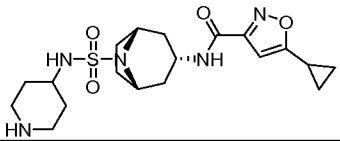
645		None	**765**		HCl
646		TFA	**766**		None
647		None			

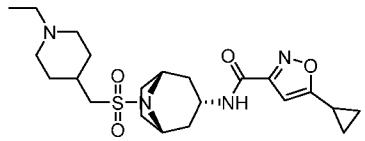
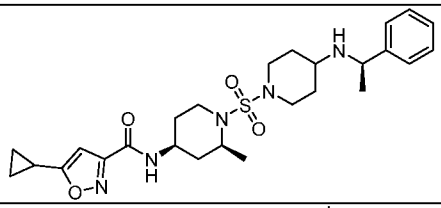
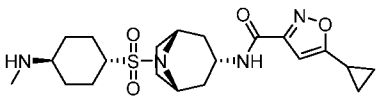
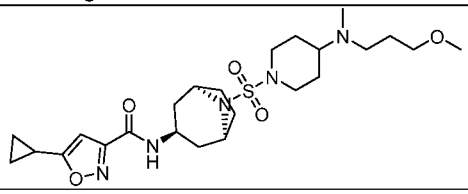
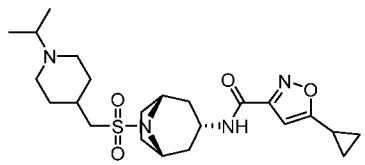
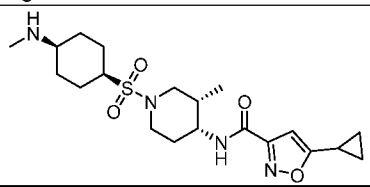
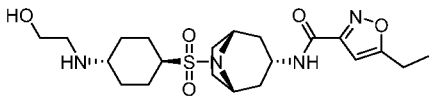
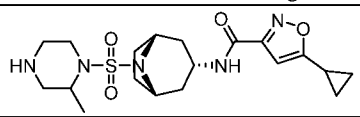
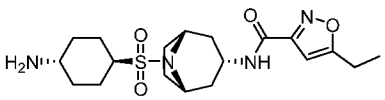
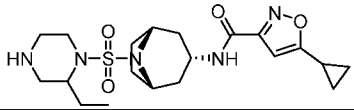
Table 3

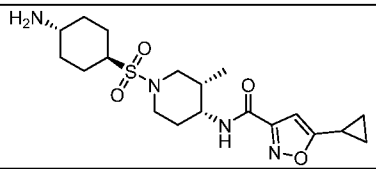
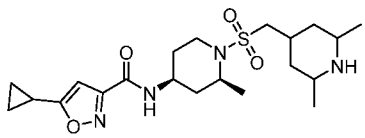
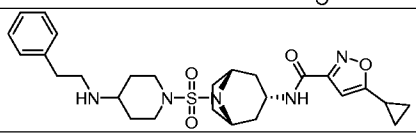
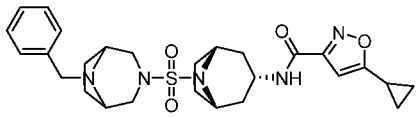
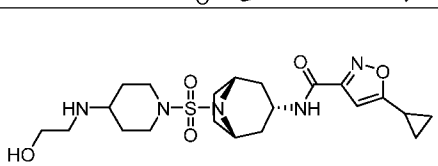
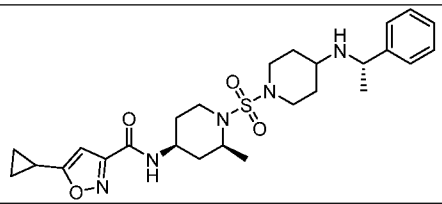
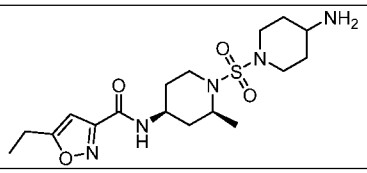
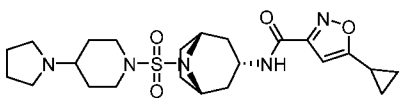
Cpd. No.	Structure	Salt Form	Cpd. No.	Structure	Salt Form
767		TFA	**880**		None
768		TFA	**881**		None
769		TFA	**882**		HCl
770		None	**883**		None
771		TFA	**884**		HCl

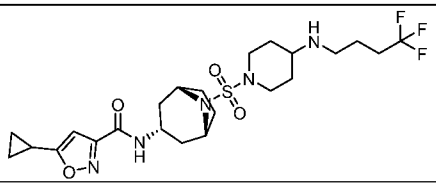
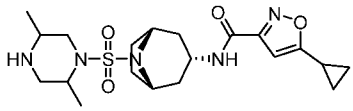
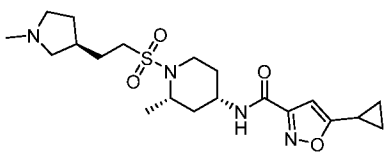
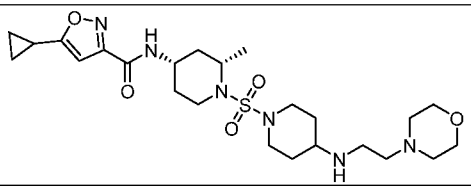
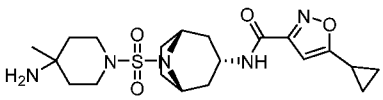
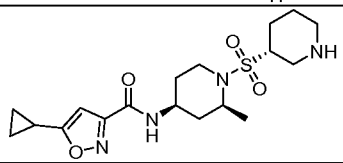
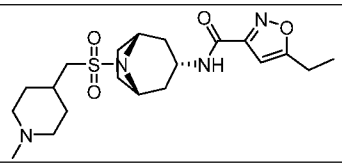
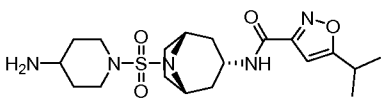
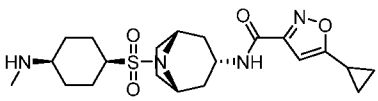
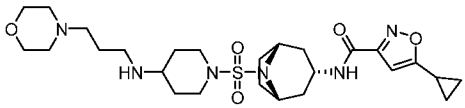
772		None	**885**		None
773		None	**886**		HCl
774		None	**887**		HCl
775		HCl	**888**		None
776		None	**889**		None

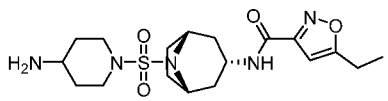
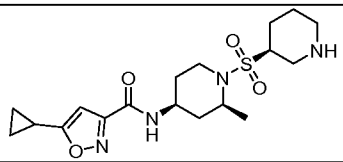
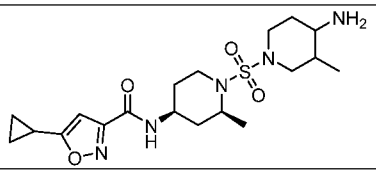
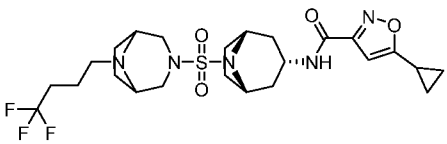
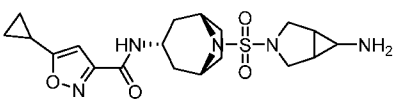
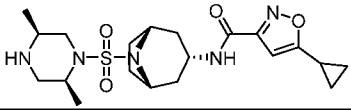
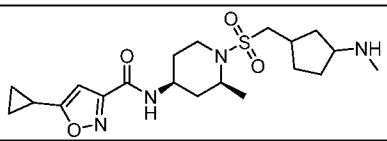
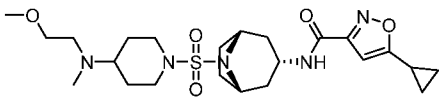
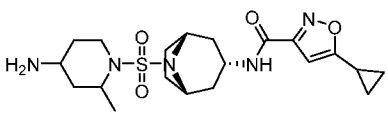
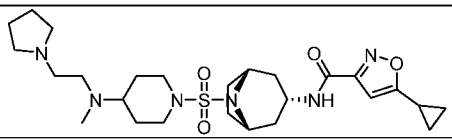
777		HCl	**890**		None
778		TFA	**891**		HCl
779		None	**892**		None
780		None	**893**		None

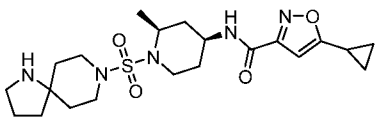
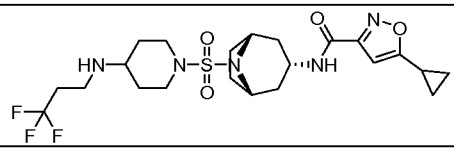
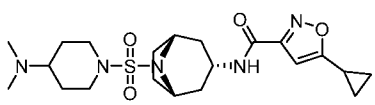
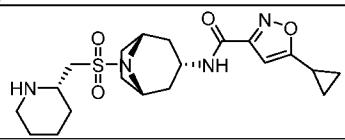
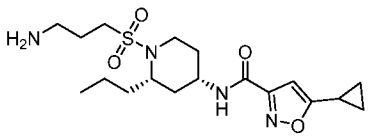
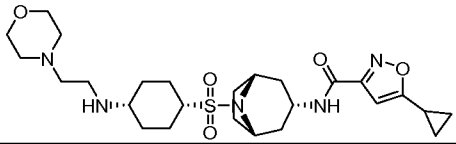
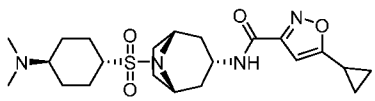
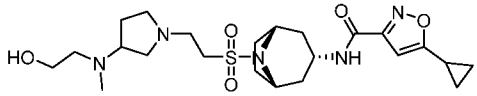
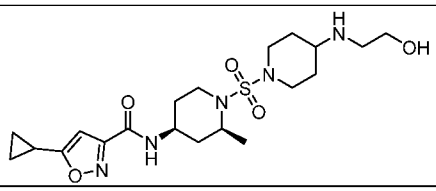
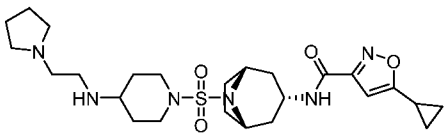
781		None	**894**		None
782		TFA	**895**		TFA
783		None	**896**		None
784		None	**897**		HCl

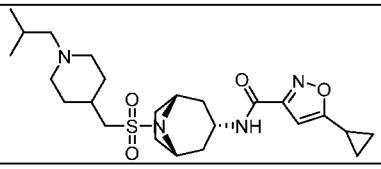
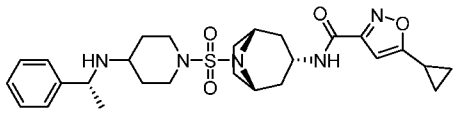
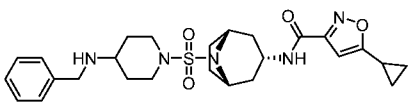
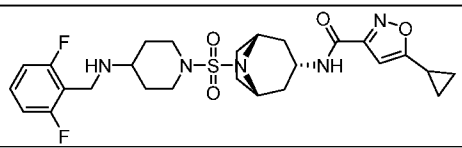
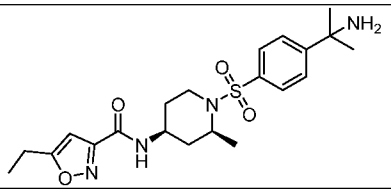
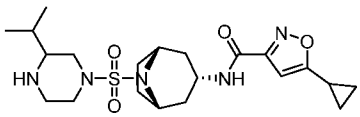
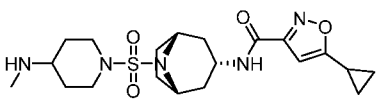
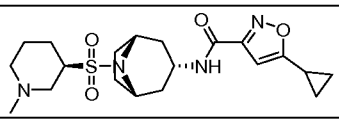
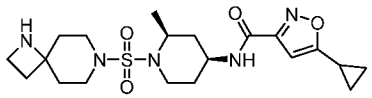
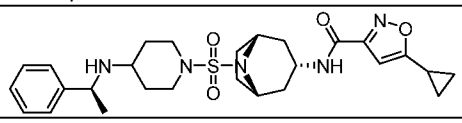
785		None	**898**		None
786		None	**899**		None
787		TFA	**900**		None
788		HCl	**901**		HCl
789		None	**902**		None

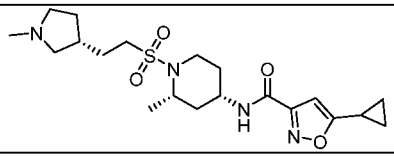
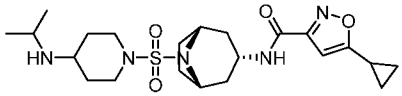
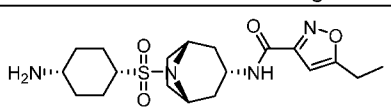
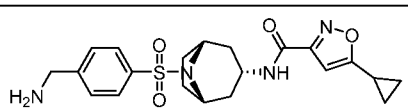
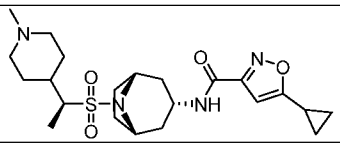
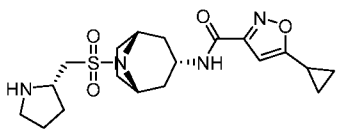
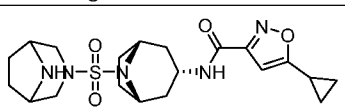
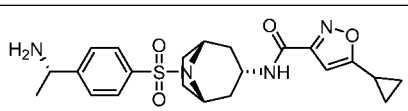
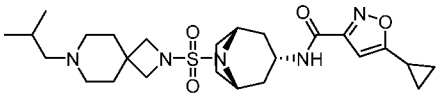
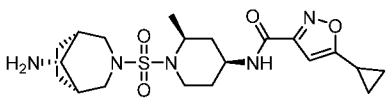
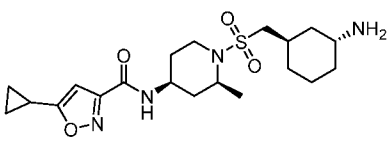
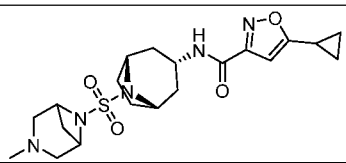
790		TFA	**903**		None
791		None	**904**		None
792		None	**905**		None
793		None	**906**		None

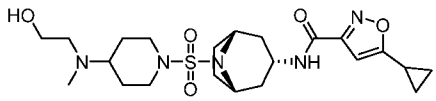
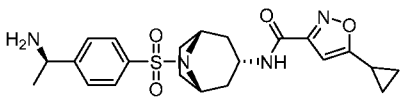
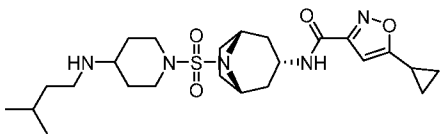
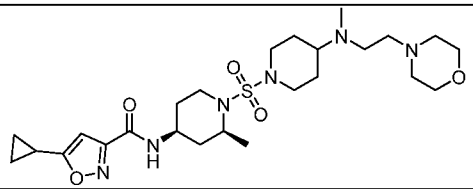
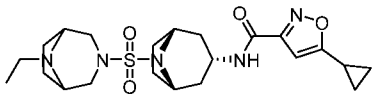
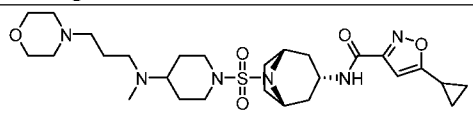
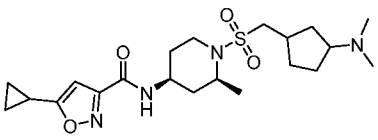
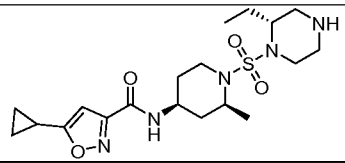
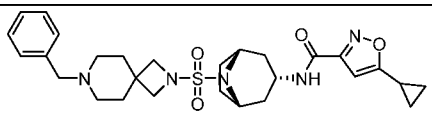
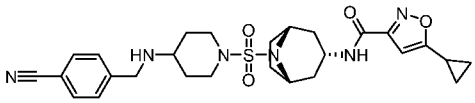
794		None	**907**		HCl
795		None	**908**		None
796		TFA	**910**		HCl
797		None	**911**		HCl
798		None	**912**		None

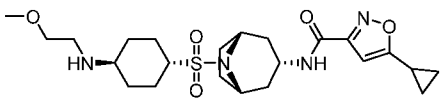
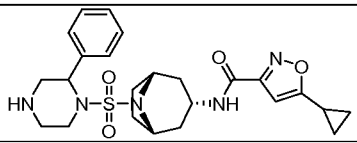
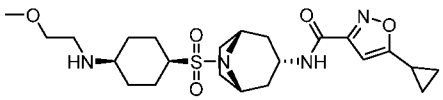
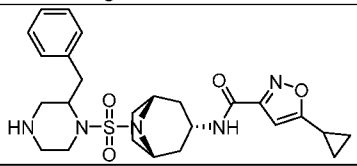
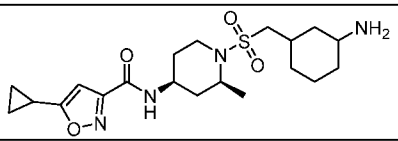
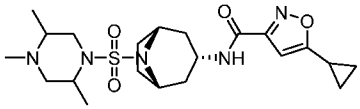
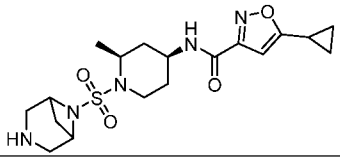
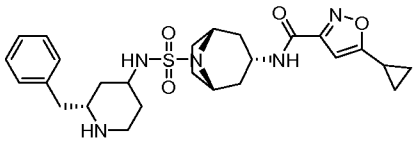
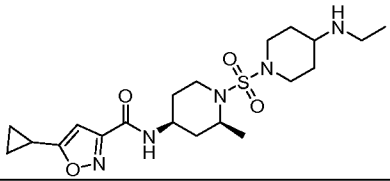
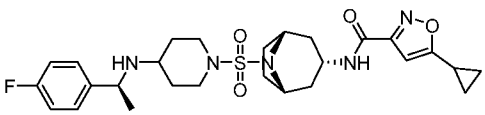
799		None	**913**		HCl
800		TFA	**914**		None
801		HCl	**915**		HCl
802		None	**916**		TFA
803		None	**917**		None

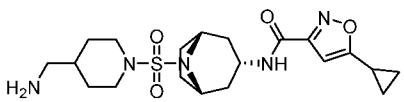
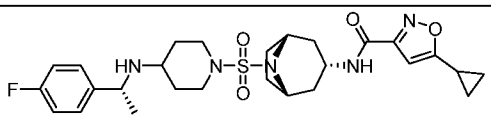
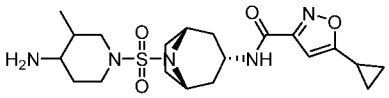
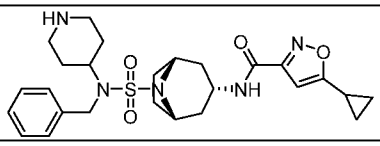
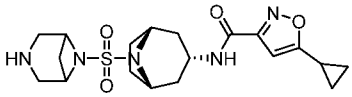
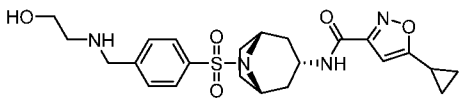
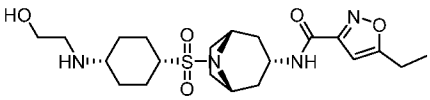
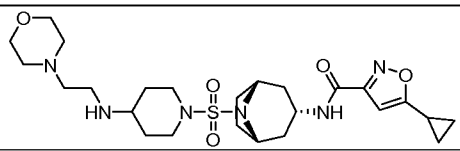
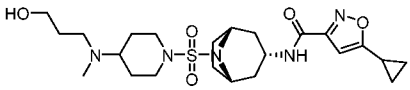
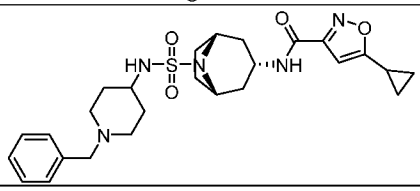
804		TFA	**918**		None
805		None	**919**		None
806		HCl	**920**		None
807		TFA	**921**		None
808		None	**922**		None

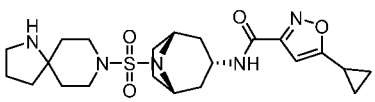
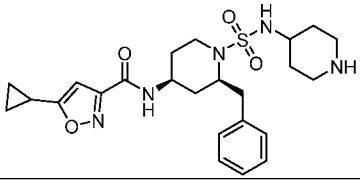
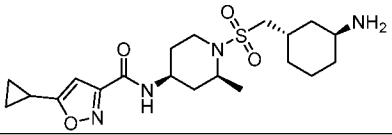
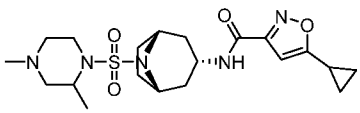
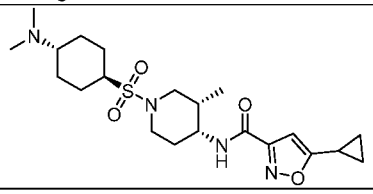
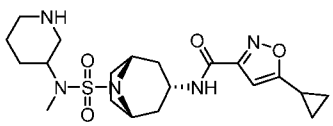
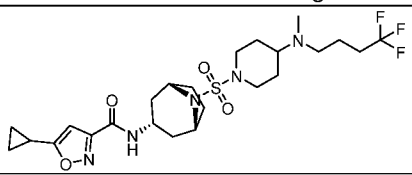
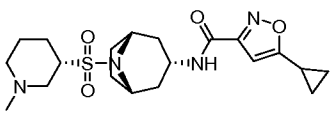
809		TFA	**923**		None
810		None	**924**		None
811		HCl	**925**		HCl
812		None	**926**		None
813		TFA	**927**		None

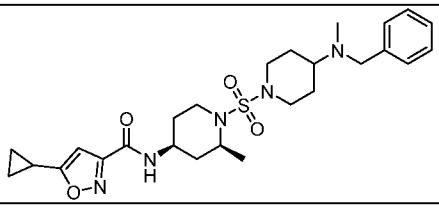
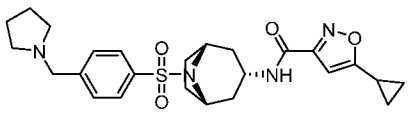
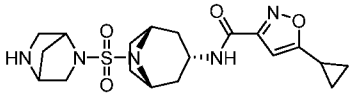
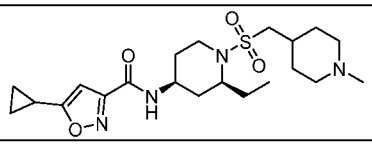
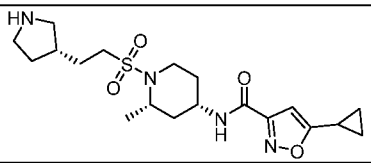
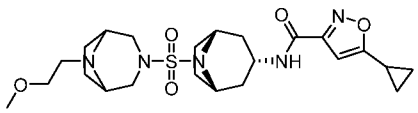
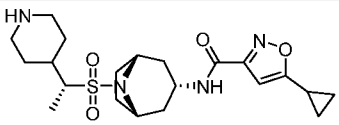
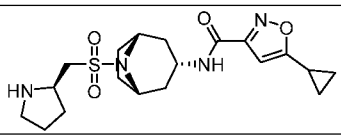
814		None	**928**		HCl
815		None	**929**		None
816		None	**930**		None
817		HCl	**931**		None
818		TFA	**932**		HCl
819		None	**933**		TFA

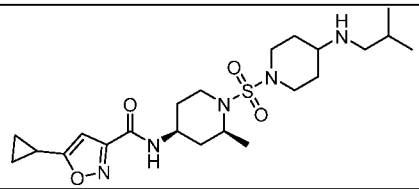
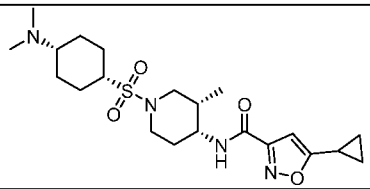
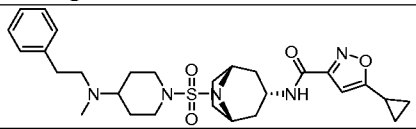
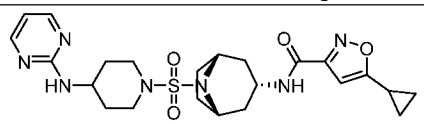
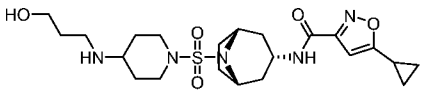
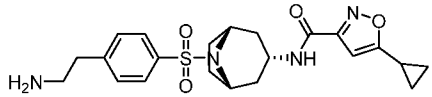
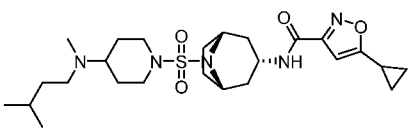
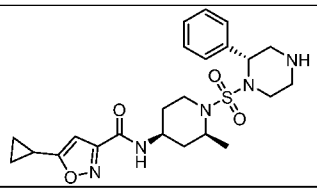
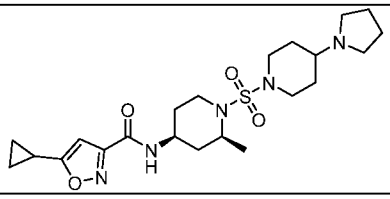
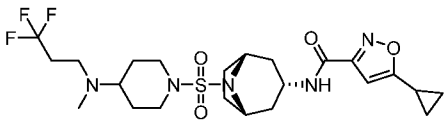
820		None	**934**		None
821		None	**935**		None
822		None	**936**		None
823		None	**937**		None
824		TFA	**938**		None

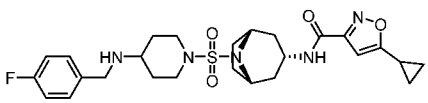
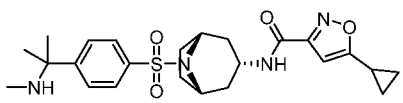
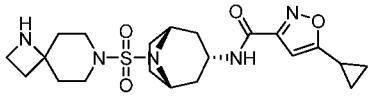
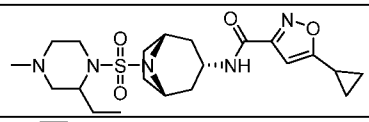
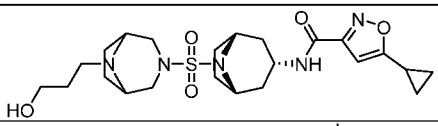
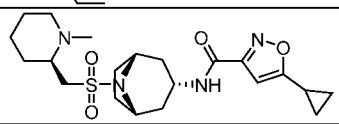
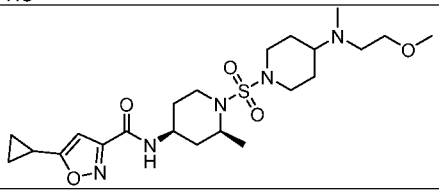
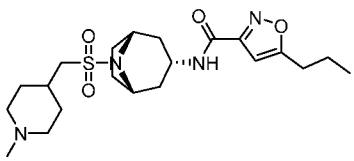
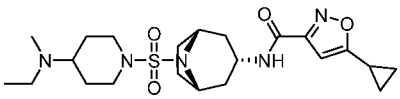
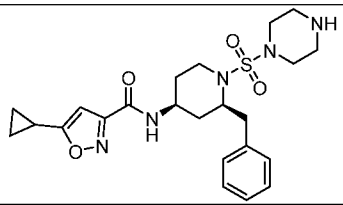
825		None	**939**		HCl
826		None	**940**		None
827		None	**941**		None
828		None	**942**		HCl
829		HCl	**943**		None

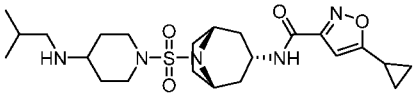
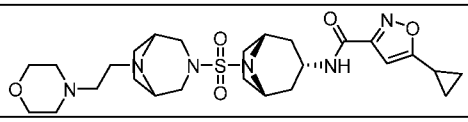
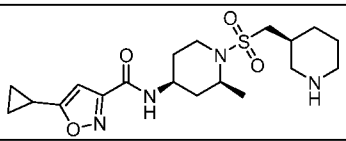
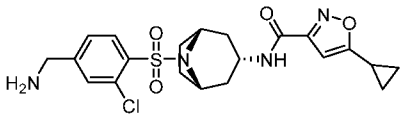
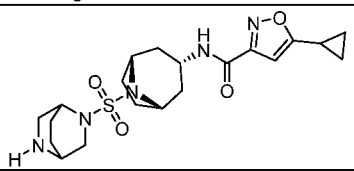
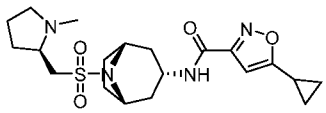
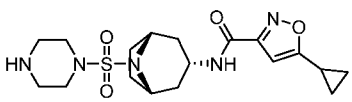
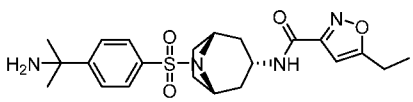
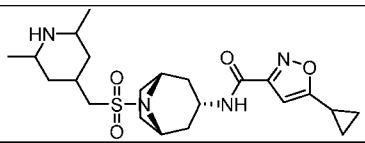
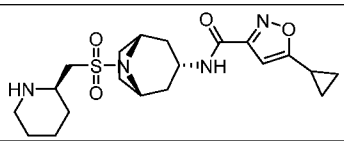
830		HCl	**944**		None
831		HCl	**945**		HCl
832		TFA	**946**		None
833		HCl	**947**		None
834		None	**948**		None

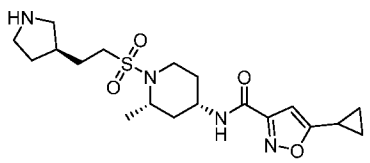
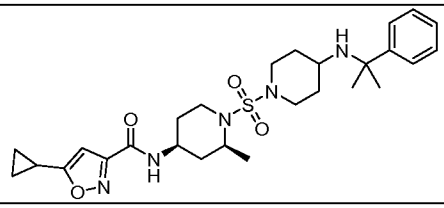
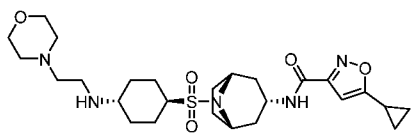
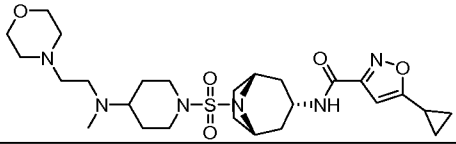
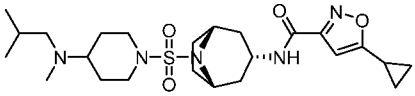
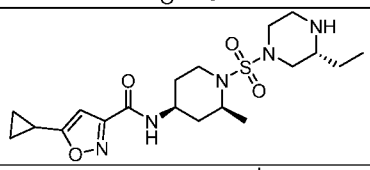
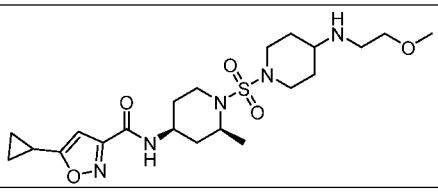
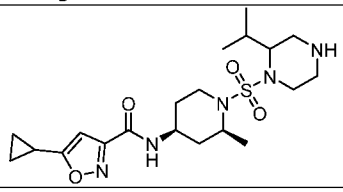
835		TFA	**949**		HCl
836		None	**950**		HCl
837		None	**951**		TFA
838		None	**952**		None

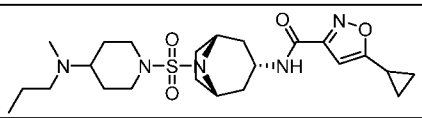
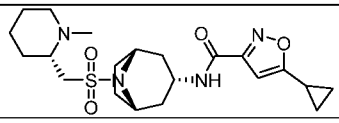
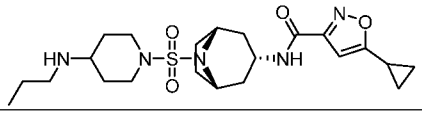
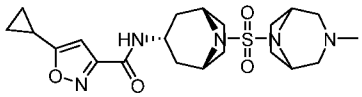
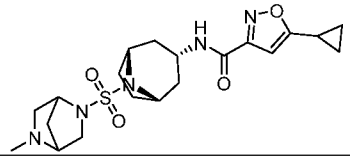
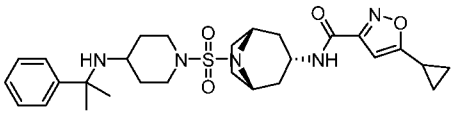
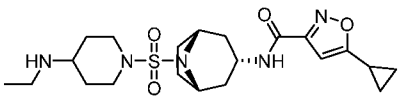
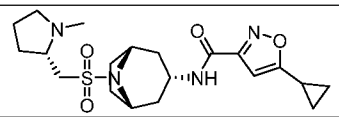
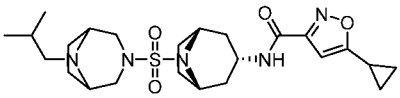
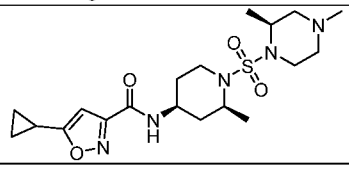
839		None	**953**		HCl
840		HCl	**954**		HCl
841		None	**955**		None
842		HCl	**956**		None

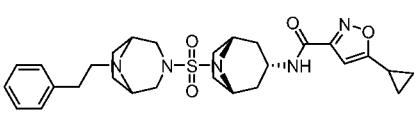
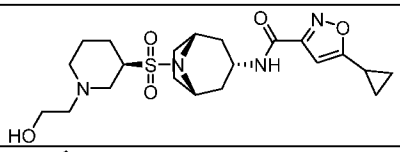
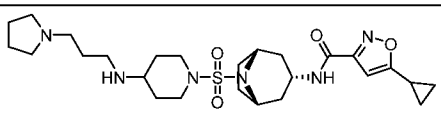
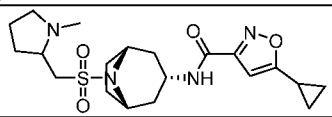
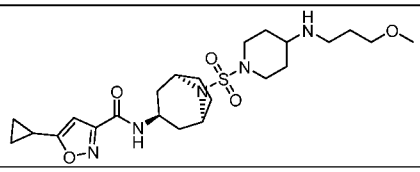
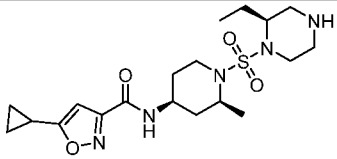
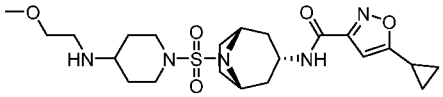
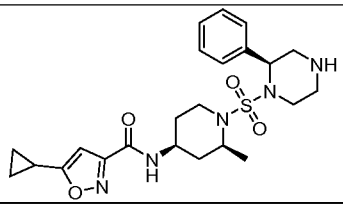
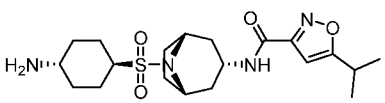
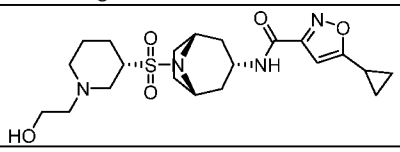
843		HCl	**957**		None
844		None	**958**		None
845		None	**959**		HCl
846		None	**960**		None
847		None	**961**		None

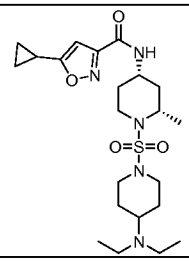
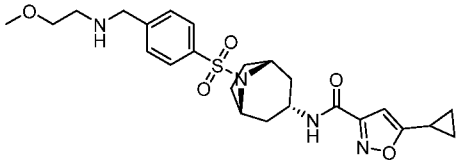
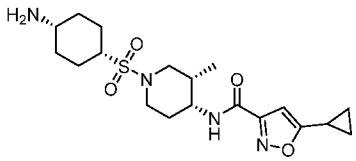
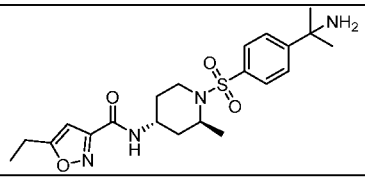
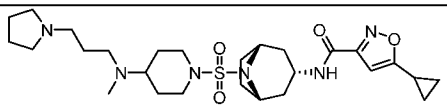
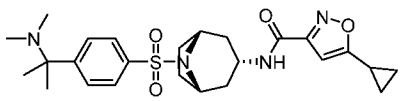
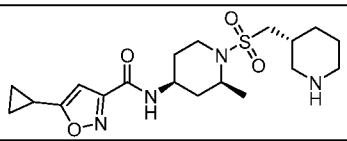
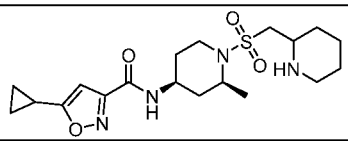
848		None	**962**		None
849		TFA	**963**		None
850		None	**964**		None
851		None	**965**		HCl
852		TFA	**966**		None

853		None	**967**		None
854		HCl	**968**		HCl
855		TFA	**969**		None
856		HCl	**970**		HCl
857		HCl	**971**		None

858		None	**972**		None
859		None	**973**		None
860		None	**974**		None
861		None	**975**		None

862		TFA	**976**		None
863		None	**977**		TFA
864		None	**978**		None
865		HCl	**979**		None
866		None	**980**		None

867		None	**981**		None
868		HCl	**982**		TFA
869		None	**983**		None
870		None	**984**		None
871		HCl	**985**		None

872		None	**986**		None
873		None	**987**		None
874		HCl	**988**		HCl
875		HCl	**989**		HCl

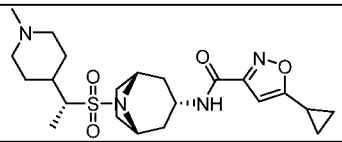
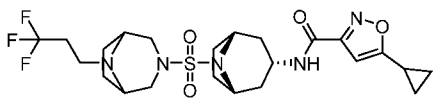
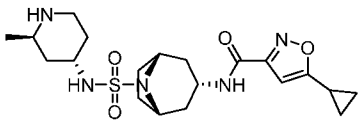
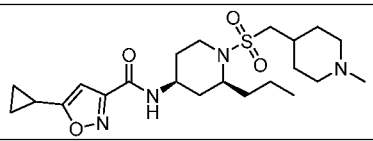
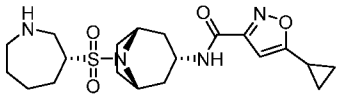
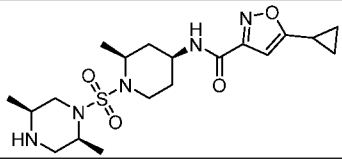
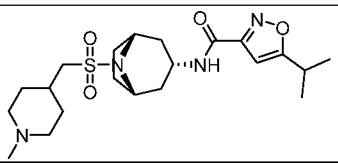
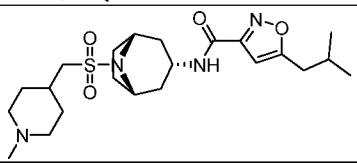
876		None	**990**		None
877		HCl	**991**		HCl
878		None	**992**		None
879		HCl	**993**		HCl

Table 1A

Cpd. No.	Chemical Name	LCMS M+H or (M+Na)	SMYD3 Biochem IC_{50} (μM)*	SMYD3 Cell IC_{50} (μM)*
1	N-(1-(L-phenylalanyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	383.5	2.87638	
2	N-(1-(D-tryptophyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	422.2	15.46877	
3	N-(1-(L-tyrosyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	399.2	0.48617	
4	5-cyclopropyl-N-(1-(glycyl-L-tryptophyl)piperidin-4-yl)isoxazole-3-carboxamide	479.4	0.94728	
5	(S)-N-(1-(2-amino-3-(4-hydroxy-3-iodophenyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	525.2	0.11601	0.80851
6	N-((2R)-1-(L-tyrosyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.15	2.9693	
7	N-((2S)-1-(L-tyrosyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.1	1.04499	
8	5-cyclopropyl-N-(1-(Na,1-dimethyl-L-tryptophyl)piperidin-4-yl)isoxazole-3-carboxamide	450.4	1.19566	
9	(S)-N-(1-(2-amino-3-(3-bromo-4-hydroxyphenyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	477.15	0.21411	
10	(R)-N-(1-(3-amino-2-benzylpropanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397.1	0.31912	1.81743
11	(S)-N-(1-(3-amino-2-benzylpropanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397.1	2.41085	
12	N-(1-(4-benzylpiperidine-4-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	438.2	1.59927	
13	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.1	1.29457	
14	(S)-N-(1-(2-amino-3-(4-hydroxyphenyl)propyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	385.1	4.59243	
15	5-cyclopropyl-N-(1-(piperidine-4-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	347.1	8.54547	

16	5-cyclopropyl-N-(1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	361.1	10.04224	
17	5-cyclopropyl-N-(1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	361.1	1.05672	
18	5-cyclopropyl-N-(1-(2-(1-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	5.07998	
19	(R)-N-(1-(2-benzyl-3-hydroxypropanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	398.1	30.89904	
20	N-(1-((1r,3r)-3-aminocyclobutane-1-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	333.15	5.77474	
21	N-(1-((1s,3s)-3-aminocyclobutane-1-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	333.1	5.69337	
24	N-((3S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375	1.99675	
25	N-((3R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375	0.29888	
26	(R)-N-(1-(3-amino-2-(4-hydroxybenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.2	5.2367	
27	(S)-N-(1-(3-amino-2-(4-hydroxybenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.2	0.34237	
28	(R)-N-(1-(3-amino-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	539.05	2.04271	
29	(S)-N-(1-(3-amino-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	539.05	0.04225	1.10146
30	(R)-5-cyclopropyl-N-(1-(2-hydroxy-3-(4-hydroxyphenyl)propyl)piperidin-4-yl)isoxazole-3-carboxamide	386.15	42.67345	
31	(R)-5-cyclopropyl-N-(1-(3-hydroxy-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	540	5.09573	
32	N-(1-((R)-3-((S)-3-aminobutanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	624	4.11464	

33	N-(1-((S)-3-((S)-3-aminobutanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	624	0.47322	
34	(R)-N-(1-(3-(3-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	1.63668	
35	(S)-N-(1-(3-(3-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	0.11659	
36	(R)-N-(1-(3-(2-aminoacetamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	596.05	9.41289	
37	(S)-N-(1-(3-(2-aminoacetamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	596.05	0.62263	
38	(R)-N-(1-(3-amino-2-(3-hydroxy-4-methylbenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	427.15	0.518	
39	(S)-N-(1-(3-amino-2-(3-hydroxy-4-methylbenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	427.15	13.98028	
40	N-(1-(3-aminopropyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	293.05	3.1591	
41	5-cyclopropyl-N-(1-(ethylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	328	13.88514	
42	N-(1-((R)-3-((R)-2-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	8.39137	
43	N-(1-((S)-3-((R)-2-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	1.23321	
44	N-(1-((R)-3-((R)-3-aminobutanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	624.05	13.80215	
45	N-(1-((S)-3-((R)-3-aminobutanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	624.05	0.47931	

46	N-(1-((3-aminopropyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.1	0.11881	1.0204
47	N-((3S)-1-(D-tyrosyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.1	14.88112	
48	N-((3R)-1-(D-tyrosyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.1	14.91848	
49	5-cyclopropyl-N-((3S)-1-glycyl-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	307	37.18839	
50	5-cyclopropyl-N-((3R,4R)-1-glycyl-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	307	9.72067	
51	5-cyclopropyl-N-((3R,4S)-1-glycyl-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	307	12.73254	
52	5-cyclopropyl-N-((2S)-1-glycyl-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	307.1	32.52331	
53	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	0.86212	
54	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	2.0772	
55	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	0.6809	
56	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	0.17163	3.18391
57	N-((2R,4R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.15	0.07164	0.94669
58	N-((2R,4S)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(397.2)	1.40209	
59	N-((2S,4S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(397.15)	7.96967	

60	N-((2S,4R)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	1.40665	
61	N-(1-((R)-3-((S)-2-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	15.29772	
62	N-(1-((S)-3-((S)-2-aminopropanamido)-2-(4-hydroxy-3-iodobenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	610.1	1.32539	
63	(R)-N-(1-(3-amino-2-(3-chloro-4-hydroxybenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.15	0.13855	1.44404
64	(S)-N-(1-(3-amino-2-(3-chloro-4-hydroxybenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.1	7.15928	
65	N-((3R)-1-((2-aminoethyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.1	0.20506	1.05134
66	N-((3S)-1-((2-aminoethyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.1	0.59032	3.71821
67	N-((3S)-1-(L-tyrosyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.1	2.32362	
68	N-((3R)-1-(L-tyrosyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413.1	1.68772	
69	5-cyclopropyl-N-((2S)-2-methyl-1-(3-(pyrrolidin-1-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	375.15	12.43914	
70	5-cyclopropyl-N-((2R)-2-methyl-1-(3-(pyrrolidin-1-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	7.72648	
71	N-((2S)-1-((1s,3R)-3-aminocyclobutane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	2.54308	
72	N-((2S)-1-((1r,3S)-3-aminocyclobutane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	2.72053	
73	N-(9-((1r,4r)-4-aminocyclohexane-1-carbonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	401.1	5.34634	
74	5-cyclopropyl-N-((2S)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	(362)	1.41476	

75	5-cyclopropyl-N-((2R)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	342.1	7.30714	
76	5-cyclopropyl-N-((3S,4S)-3-ethyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.3	0.54092	
77	N-((2R)-1-((2-aminoethyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.1	0.63328	2.90646
78	N-((2S)-1-((2-aminoethyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.05	0.15511	0.79154
79	(R)-N-(1-(2-amino-3-(4-hydroxyphenyl)propyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	385.1	20.42345	
80	N-(1-(3-aminopropanoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	321.1	6.81137	
81	5-cyclopropyl-N-((2R)-1-glycyl-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	307.1	22.11145	
82	N-((2S,4S)-1-(3-aminopropanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	321.1	10.50574	
83	N-((2S,4R)-1-(3-aminopropanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	321.1	6.59727	
84	N-((2R)-1-(3-aminopropanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	321.1	6.14386	
85	N-((2S)-1-((1R,3R)-3-aminocyclopentane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.2	2.36831	
86	N-((2S)-1-((1R,3S)-3-aminocyclopentane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.2	2.56375	
87	N-((2R)-1-((1s,3S)-3-aminocyclobutane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	3.25213	
88	N-(2-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-azabicyclo[2.2.2]octan-5-yl)-5-cyclopropylisoxazole-3-carboxamide	387	0.15617	2.49959
89	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	437.1	3.3857	

90	5-cyclopropyl-N-((2S)-2-methyl-1-((1r,4S)-4-(methylamino)cyclohexane-1-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	389.15	5.33028	
91	5-cyclopropyl-N-((2S)-2-methyl-1-(2-(piperazin-1-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	376.15	3.91293	
92	5-cyclopropyl-N-((2R)-2-methyl-1-(2-(piperazin-1-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	376.15	0.77789	
93	N-((3S,4S)-1-(4-aminocyclohexane-1-carbonyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	1.61465	
94	N-((2S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.1	2.37948	
95	N-((2R)-1-((1R,3R)-3-aminocyclopentane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(383.15)	0.53208	
96	N-((2R)-1-((1R,3S)-3-aminocyclopentane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.1	1.89956	
97	N-((2R)-1-((1r,3R)-3-aminocyclobutane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	0.77892	
98	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-propylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	403.1	0.65544	
99	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-isopropylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	403.1	0.23028	3.05094
100	N-(5-((1r,4r)-4-aminocyclohexane-1-carbonyl)-5-azaspiro[3.5]nonan-8-yl)-5-cyclopropylisoxazole-3-carboxamide	(423.2)	2.20456	
101	N-((1R,3S,5S)-8-((1r,4R)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	(409.2)	>10	
102	N-((1R,3R,5S)-8-((1r,4R)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	387.1	0.10577	1.70139
103	N-((2S)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.2	1.44518	
104	N-((2R)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.2	0.56589	

105	5-cyclopropyl-N-((2S)-1-((1r,4S)-4-(dimethylamino)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	403.1	19.98827	
106	N-((2S)-1-((1S,3S)-3-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	3.52143	
107	5-cyclopropyl-N-((2R)-2-methyl-1-(piperidine-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	361.2	2.51548	
108	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.3	1.42279	
109	N-(2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.2	0.09677	1.92675
110	N-((2R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.1	0.09941	0.89293
111	(S)-N-(1-(3-amino-2-(4-hydroxy-3-(trifluoromethyl)benzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	481	2.46875	
112	(R)-N-(1-(3-amino-2-(4-hydroxy-3-isopropylbenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	455.1	1.09349	
113	N-((2R)-1-(((1r,4R)-4-aminocyclohexyl)methyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.2	4.58751	
114	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2,2-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	1.30613	
115	5-cyclopropyl-N-((2S)-2-methyl-1-(2-(4-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.2	0.4717	
116	5-cyclopropyl-N-((2R)-2-methyl-1-(2-(4-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	2.9085	
117	N-((2S)-1-((1S,3R)-3-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.25	5.60335	
118	N-((2R)-1-((2R,5S)-5-aminotetrahydro-2H-pyran-2-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	377.25	0.20786	1.35148

119	ethyl 4-(5-cyclopropylisoxazole-3-carboxamido)-1-(2-(piperidin-4-yl)acetyl)piperidine-3-carboxylate	433.3	2.99148	
120	(R)-N-(1-(3-amino-2-(4-hydroxy-3-(trifluoromethyl)benzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	481.1	0.08157	
121	(S)-N-(1-(3-amino-2-(4-hydroxy-3-isopropylbenzyl)propanoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	455.2	0.00957	0.68
122	N-((2R)-1-(4-aminopiperidine-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	376.1	0.85107	
123	N-(2-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2-azabicyclo[2.2.1]heptan-5-yl)-5-cyclopropylisoxazole-3-carboxamide	373.1	1.16837	
124	5-cyclopropyl-N-((2R)-2-methyl-1-((1r,4R)-4-(methylamino)cyclohexane-1-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	389	0.27407	2.24358
125	5-cyclopropyl-N-(9-(2-(piperidin-4-yl)acetyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	401.1	7.75656	
126	5-cyclopropyl-N-((1R,3s,5S)-8-(2-(piperidin-4-yl)acetyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	387.1	9.85627	
127	5-cyclopropyl-N-((1R,3r,5S)-8-(2-(piperidin-4-yl)acetyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	387.1	1.27842	
128	N-((2S)-1-(2-(8-azabicyclo[3.2.1]octan-3-yl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	401.25	0.84351	
129	N-((2R)-1-(2-(8-azabicyclo[3.2.1]octan-3-yl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	401.1	0.59462	
130	N-((2S)-1-(6-aminospiro[3.3]heptane-2-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	387.1	1.30431	
131	N-((2S)-1-((2R,5S)-5-aminotetrahydro-2H-pyran-2-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	377.1	2.08144	
132	5-cyclopropyl-N-((2S)-2-methyl-1-(piperidine-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	361.2	5.54521	

133	N-((2S)-1-((R)-5-amino-3-hydroxypentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	365.1	6.23726	
134	N-((2R)-1-((R)-5-amino-3-hydroxypentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	365.2	1.85646	
135	5-cyclopropyl-N-((2R)-1-(5-hydroxypiperidine-3-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	377.1	2.48647	
136	5-cyclopropyl-N-((2R)-2-methyl-1-(6-azaspiro[2.5]octane-1-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	387.1	0.75897	
137	5-cyclopropyl-N-((2R)-1-((1r,4R)-4-hydroxycyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	376.25	41.16974	
138	N-((2S)-1-(((1r,4S)-4-aminocyclohexyl)methyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	361.1	4.30775	
139	5-cyclopropyl-N-((2R)-1-((1r,4R)-4-(dimethylamino)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	403.1	1.6468	
140	5-cyclopropyl-N-((2R)-2-methyl-1-(2-(3-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.25	0.84236	
141	5-cyclopropyl-N-((2S)-2-methyl-1-(2-(2-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.35	3.52551	
142	N-((2S)-1-(4-aminobutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.1	3.64524	
143	N-((2R)-1-((1S,3R)-3-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	1.98991	
144	5-cyclopropyl-N-((2R)-2-methyl-1-(6-azaspiro[3.4]octane-2-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	387.25	0.54601	
145	N-(1-((1R,3R)-3-aminocyclopentane-1-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	5.97994	
146	N-((3R,4R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.3	2.27591	

147	5-cyclopropyl-N-((3R,4R)-3-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	1.52725	
148	N-((3R,4S)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.3	0.28218	1.81302
149	5-cyclopropyl-N-((3R,4S)-3-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	0.29052	3.22445
150	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-4-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	0.90972	
151	ethyl 1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-3-carboxylate	433.3	3.53948	
152	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-3,3-difluoropiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397.1	2.2474	
153	5-cyclopropyl-N-(4-methyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	375.3	0.8483	
154	5-cyclopropyl-N-(3,3-difluoro-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	397.1	1.55665	
155	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-3,3-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.3	0.57463	
156	N-(5-((1r,4r)-4-aminocyclohexane-1-carbonyl)-5-azaspiro[2.5]octan-8-yl)-5-cyclopropylisoxazole-3-carboxamide	387.2	0.24493	1.75569
157	5-cyclopropyl-N-(3,3-dimethyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.3	0.52149	
158	N-(1-(4-aminobutanoyl)-4-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.2	7.3363	
159	ethyl (2S)-1-(4-aminobutanoyl)-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-2-carboxylate	393.2	25.18182	
160	ethyl 1-(4-aminobutanoyl)-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-3-carboxylate	393.2	2.23333	
161	N-(1-(4-aminobutanoyl)-3,3-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.3	1.25033	

162	N-((2S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	437.3	>10	
163	N-((2R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	437.25	7.16633	
164	5-cyclopropyl-N-((2R)-2-methyl-1-(2-methyl-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	403.1	5.90922	
165	5-cyclopropyl-N-((2S)-2-methyl-1-(2-methyl-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	403.1	4.73168	
166	5-cyclopropyl-N-((2R)-2-methyl-1-(2-(2-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	0.50622	
167	5-cyclopropyl-N-((2R)-1-(2-(4-hydroxypiperidin-4-yl)acetyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	391.2	0.91127	
168	5-cyclopropyl-N-((2R)-1-(4-ethylpiperidine-4-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	389.1	3.17831	
169	5-cyclopropyl-N-((2S)-1-(4-ethylpiperidine-4-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	389.1	3.77384	
170	5-cyclopropyl-N-((2R)-1-(4-fluoropiperidine-4-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	379.1	0.6767	
171	N-((2R,4R)-1-(4-aminobutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.1	3.11011	
172	N-((2R,4R)-1-(4-amino-3-hydroxybutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	351.1	6.77783	
173	N-((2S)-1-(4-amino-3-hydroxybutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	351.1	5.26362	
174	N-((2R)-1-((1S,3S)-3-aminocyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	0.72766	
175	N-((2R)-1-(6-aminospiro[3.3]heptane-2-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	387.1	0.27354	0.98285

176	5-cyclopropyl-N-((2S)-2-methyl-1-(3-(pyrrolidin-3-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	375.1	0.62421	
177	5-cyclopropyl-N-((2S)-1-(5-hydroxypiperidine-3-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	377.2	>10	
178	5-cyclopropyl-N-((2S)-2-methyl-1-(6-azaspiro[3.4]octane-2-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	387.1	2.02272	
179	5-cyclopropyl-N-((2S)-2-methyl-1-(6-azaspiro[2.5]octane-1-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	387.25	1.42245	
180	5-cyclopropyl-N-((2R)-2-methyl-1-(3-(pyrrolidin-3-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	375.25	0.95346	
181	N-(9-((3-aminopropyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	397	0.09267	0.56598
182	N-(1-((1R,3S)-3-aminocyclopentane-1-carbonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	4.7946	
183	N-(1-((2-aminoethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	343	1.42123	
184	N-((2R,4S)-1-(5-aminopentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.2	2.67277	
185	N-((2R,4S)-1-(benzylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	404.15	4.30641	
186	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	396.1	>10	
187	N-((2S,4S)-1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.1	0.00409	0.83104
188	N-((2S,4R)-1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.1	0.07229	
189	N-((2R,4R)-1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.1	0.05594	1.24113
190	N-((3R,4S)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.1	0.352	

191	N-(8-((1r,4r)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	387.2	>10	
192	ethyl (2S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-2-carboxylate	433.1	7.08316	
193	N-((3R,4S)-1-(4-aminobutanoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.2	2.86619	
194	N-((3S,4R)-1-(4-aminobutanoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.2	1.36537	
195	N-((3R,4R)-1-(4-aminobutanoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.2	>10	
196	N-((3S,4S)-1-(4-aminobutanoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.2	6.90946	
197	N-(1-(4-aminobutanoyl)-3,3-difluoropiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.1	>10	
198	N-(5-(4-aminobutanoyl)-5-azaspiro[2.5]octan-8-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	0.82956	
199	N-(8-(4-aminobutanoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	0.67809	
201	N-((2S)-1-(4-aminopiperidine-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	376.1	2.22535	
202	N-((2R)-1-(4-aminocubane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	395.1	0.14195	1.30843
203	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2,3-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.25	0.37891	
204	N-((2S)-1-(2-(1-(aminomethyl)cyclobutyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.25	4.67985	
205	N-((2R)-1-(2-(1-(aminomethyl)cyclobutyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	375.1	1.99119	
206	5-cyclopropyl-N-((2S)-2-methyl-1-(2-(3-methylpiperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	1.58733	

207	5-cyclopropyl-N-((2S)-1-(4-fluoropiperidine-4-carbonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	379.2	2.60074	
208	N-((2R,4S)-1-(4-aminobutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	335.1	3.81793	
209	N-((2R,4S)-1-((3-aminopropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.15	0.1003	
210	N-(1-((3-aminopropyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	357.1	0.32133	2.90138
211	N-(9-(4-aminobutanoyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	361.1	5.85206	
212	N-((2R,4R)-1-(5-aminopentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.15	0.83765	
213	5-cyclopropyl-N-((2R,4S)-1-(cyclopropylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	354	>10	
214	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(N-methylsulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	343	>10	
215	5-cyclopropyl-N-((2R,4S)-1-((2-methoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	(394.1)	>10	
216	5-cyclopropyl-N-((2R,4R)-1-(cyclopropylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	354	>10	
217	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(N-methylsulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	343.1	6.75805	
218	N-(1-((3-aminopropyl)sulfonyl)-4-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.2	0.23041	1.4182
219	N-(1-(4-aminobutanoyl)-2-(tert-butyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	377.2	6.31559	
220	N-((3R,4R)-1-(4-aminobutanoyl)-3-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397.2	2.52191	
221	N-((3R,4S)-1-(4-aminobutanoyl)-3-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397.1	>10	

222	N-((2S)-1-(4-aminocubane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	395.1	4.63995	
223	5-cyclopropyl-N-((2S)-1-(2-(4-hydroxypiperidin-4-yl)acetyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	391.1	7.18894	
224	5-cyclopropyl-N-((2R)-2-methyl-1-(4-methylpiperidine-4-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	375.15	1.41743	
225	N-((2R,4S)-1-(4-amino-3-hydroxybutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	351.1	9.0491	
226	N-((2S)-1-(2-(3-aminocyclohexyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.1	2.38426	
227	N-(1-(2-(1H-imidazol-4-yl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	358.1	>10	>40
228	N-((2S,4S)-1-(5-aminopentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.15	1.28279	
229	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(propylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	356	0.8625	
230	5-cyclopropyl-N-((2S,4S)-1-(isobutylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	370.1	0.47239	
231	ethyl 2-(((2S,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)acetate	400.1	1.16807	
232	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	396.1	3.26173	
233	5-cyclopropyl-N-((2S,4S)-1-((2-methoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	372	2.36218	
234	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	394	1.2429	
235	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(phenethylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	418	1.33318	3.2982
236	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3,3,3-trifluoropropyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	410.05	1.03937	

237	5-cyclopropyl-N-((2S,4S)-1-((2-isopropoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	400	3.46488	
238	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(propylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	356.05	>10	
239	5-cyclopropyl-N-((2R,4S)-1-(isobutylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	370.1	>10	
240	N-((2R,4S)-1-(butylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	370.1	>10	
241	N-((2R,4S)-1-((6-chloropyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.05	>10	
242	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(pyrrolidin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	383.15	>10	
243	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412.15	1.75762	
244	N-((2S,4R)-1-(benzylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	404	>10	14.06578
245	ethyl 2-(((2S,4R)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)acetate	400.1	>10	
246	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	396	>10	
247	5-cyclopropyl-N-((2S,4R)-1-(cyclopropylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	354.1	>10	
248	5-cyclopropyl-N-((2S,4R)-1-((2-methoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	372.1	>10	
249	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(propylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	356.1	>10	
250	5-cyclopropyl-N-((2R,4R)-1-(isobutylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	370.15	9.44683	
251	N-((2R,4R)-1-(butylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	370.1	6.15252	

252	ethyl 2-(((2R,4R)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)acetate	400.05	>10	
253	N-((2R,4R)-1-((6-chloropyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.1	>10	
254	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(pyrrolidin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	383.15	4.13805	
255	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412.1	1.19523	
256	methyl 3-(((2R,4R)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)propanoate	400.1	>10	
257	5-cyclopropyl-N-((2R,4R)-1-((2-methoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	372	9.2914	
258	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((3,3,3-trifluoropropyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	410	8.37154	
259	5-cyclopropyl-N-((2R,4R)-1-((3-methoxypropyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	386.15	>10	
260	5-cyclopropyl-N-((2S,4S)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	341.9	2.44732	
261	5-cyclopropyl-N-((2R,4R)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	342	>10	
262	5-cyclopropyl-N-((2S,4R)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	342.05	>10	
263	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	0.03219	0.56899
264	N-((2R)-1-(2-(3-aminocyclohexyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389	0.40966	
265	N-(2-(4-aminobutanoyl)-2-azabicyclo[2.2.2]octan-5-yl)-5-cyclopropylisoxazole-3-carboxamide	347.1	5.44619	>40
266	N-((2S,4R)-1-(2-(1-(aminomethyl)cyclohexyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	403.1	>10	

267	N-((2R,4S)-1-(2-(1-(aminomethyl)cyclohexyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	403.1	8.51913	
268	N-((2R,4S)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.1	3.15461	
269	N-((2S,4S)-1-(4-amino-3-benzylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.2	>10	>40
270	N-((2R,4S)-1-(4-amino-3-benzylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.2	>10	>40
271	N-((2S,4R)-1-(4-amino-3-benzylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.2	>10	>40
272	N-((2R,4R)-1-(4-amino-3-benzylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.2	>10	>40
273	N-((2S,4R)-1-(5-aminopentanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.15	7.82701	
274	N-((2S,4S)-1-(benzylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(426.1)	0.43325	1.41883
275	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(pyridin-2-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391.05	0.1537	0.67609
276	5-cyclopropyl-N-((2S,4S)-1-(cyclopropylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	354	3.63356	
277	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(pyrrolidin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	383	0.65372	
278	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(N-methylsulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	343	2.89251	
279	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.08154	0.26586
280	methyl 3-(((2S,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)propanoate	400	4.85331	
281	5-cyclopropyl-N-((2S,4S)-1-((3-methoxypropyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	386	1.86694	

282	methyl 3-(((2R,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)propanoate	400	>10	
283	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	394	>10	>40
284	5-cyclopropyl-N-((2R,4S)-1-((3-methoxypropyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	386.15	>10	
285	5-cyclopropyl-N-((2R,4S)-1-((2-isopropoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	400	>10	
286	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(pyridin-2-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391.05	>10	10.65927
287	N-((2S,4R)-1-((6-chloropyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425	>10	
288	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(pyrrolidin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	383.1	>10	
289	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(N-methylsulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	343	>10	
290	methyl 3-(((2S,4R)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)propanoate	400	>10	
291	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	394	>10	>40
292	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((3,3,3-trifluoropropyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	410	>10	
293	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(pyridin-2-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391.05	4.84236	7.19436
294	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	394	>10	>40
295	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(phenethylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	418.1	>10	>40

296	5-cyclopropyl-N-((2R,4R)-1-((2-isopropoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	400	5.96704	
297	N-((3R,4S)-1-(4-aminobutanoyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.1	1.80484	
298	N-((3R,4R)-1-(4-aminobutanoyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.1	6.09665	
299	N-((3S,4R)-1-(4-aminobutanoyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.1	0.98944	
300	N-((3S,4S)-1-(4-aminobutanoyl)-3-ethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.1	3.60037	
301	N-(1-(4-aminobutanoyl)-1-azaspiro[5.5]undecan-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	6.46534	
302	N-((2S,6R)-1-(4-aminobutanoyl)-2,6-diethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	377.3	6.93186	
303	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-3,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.1	1.78233	
304	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-3-(trifluoromethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	429.1	2.03567	
305	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((S)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.2	1.16784	
306	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((R)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.2	0.85247	
307	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((S)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	0.92847	
308	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((R)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	0.17867	
309	N-((2R,4R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.3	1.18016	16.79585

310	N-((2S,4S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.4	0.73318	8.10326
311	N-((2S,4R)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.1	1.61667	
312	N-((2R,4R)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.1	0.4155	
313	N-((2R,4S)-1-(4-amino-3-phenylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.2	5.02398	
314	N-((2R,4R)-1-(4-amino-3-phenylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	4.72554	>40
315	5-cyclopropyl-N-((2S,4S)-1-(N,N-dimethylsulfamoyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	(379.1)	1.32822	4.84171
316	N-((2S,4S)-1-(butylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	370.2	0.23719	0.78207
317	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(pyridin-3-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391	0.68629	4.10919
318	N-((2S,4S)-1-((6-chloropyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.1	1.88386	
319	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((pyridin-3-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	405	1.42682	4.52678
320	ethyl 2-(((2R,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-yl)sulfonyl)acetate	400.05	>10	
321	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(pyridin-2-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391	4.46652	
322	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(propylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	356	>10	
323	5-cyclopropyl-N-((2S,4R)-1-(isobutylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	370.3	>10	
324	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412.2	1.64608	

325	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((pyridin-3-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	405	>10	
326	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(phenethylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	418	>10	
327	5-cyclopropyl-N-((2S,4R)-1-((3-methoxypropyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	386	>10	
328	5-cyclopropyl-N-((2R,4R)-1-(N,N-dimethylsulfamoyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	357.15	6.91182	15.20884
329	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((pyridin-3-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	405	6.42224	20.04736
330	N-((2R,4R)-1-((4-acetamidophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.2	>10	29.32443
331	ethyl 1-((3-aminopropyl)sulfonyl)-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-3-carboxylate	429.2	0.14739	2.30591
332	N-(1-(4-aminobutanoyl)-3,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	349.2	2.53113	
333	N-((2R,4R)-1-(4-aminobutanoyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	>10	>40
334	N-((2S,4R)-1-(4-aminobutanoyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	1.89516	33.02657
335	N-((2R,4S)-1-(4-aminobutanoyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	1.11818	19.61527
336	N-((2S,4S)-1-(4-aminobutanoyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	0.05412	1.62405
337	N-((2S,4S)-1-(4-amino-3,3-dimethylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	363.1	0.96148	12.99612
338	N-((2S,4S)-1-(4-amino-3-phenylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.1	0.8416	
339	N-((2S,4R)-1-(4-amino-3-phenylbutanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.1	4.66558	

340	N-((2S,4S)-1-(1H-benzo[d]imidazole-5-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	394.2	>10	>40
341	N-((2R,4R)-1-(1H-benzo[d]imidazole-5-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	394.2	1.00187	6.0106
342	N-((2R,4R)-1-(3-(aminomethyl)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	0.55215	
343	N-((2R,4S)-1-(3-(aminomethyl)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.25	1.06666	
344	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(phenethylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	418.2	>10	
345	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((3,3,3-trifluoropropyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	410	>10	
346	5-cyclopropyl-N-((2S,4R)-1-(N,N-dimethylsulfamoyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	357.15	>10	
347	N-((2S,4R)-1-(butylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	370	8.02269	
348	N-((2S,4S)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.1	0.02251	0.83834
349	N-((2R,4R)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.1	2.26536	>40
350	5-cyclopropyl-N-((2R,4S)-1-(ethylsulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	451.2	>10	
351	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	390	3.09195	7.83322
352	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	390	0.15159	0.99614
353	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	390.1	3.97616	
354	N-((2R,4R)-1-((3-cyanophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(437.15)	1.13679	5.65265

355	N-((2R,4S)-1-((3-cyanophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	415	0.27778	
356	N-(1-(4-aminobutanoyl)-3-(trifluoromethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	1.21465	
357	N-((2R)-1-((R)-3-amino-2-(4-hydroxybenzyl)propanoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	427.1	1.1652	
358	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((S)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	3.39874	
359	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((R)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	1.4568	
360	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((S)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	0.79171	8.2842
361	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((R)-2-(piperidin-4-yl)propanoyl)piperidin-4-yl)isoxazole-3-carboxamide	389.1	1.36293	13.61968
362	5-cyclopropyl-N-((3S,4R)-3-(hydroxymethyl)-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	391.1	2.95081	
363	N-((2R,4R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-(hydroxymethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	391.1	1.98513	
364	N-((2R,4S)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.2	4.56731	
365	N-((2R,4R)-1-(3-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.3	0.45355	3.88138
366	N-((2S,4R)-1-(3-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.25	2.75278	
367	N-((2S,4S)-1-(3-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.5	4.28845	30.57389
368	N-((2R,4R)-1-(4-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.3	0.12223	1.0362

369	N-((2S,4R)-1-(4-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(433.1)	5.87044	
370	N-((2S,4S)-1-(4-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.3	4.39381	>40
371	N-((2R,4S)-1-(4-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(433.1)	4.9531	
372	N-((2S,4R)-1-(3-(aminomethyl)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	5.88826	
373	N-((2S,4S)-1-(3-(aminomethyl)cyclohexane-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	2.46688	29.7807
374	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((pyridin-3-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	405	>10	
375	N-((2R,4S)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.3	1.82988	
376	N-((2S,4R)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.3	1.32288	
377	N-((2S,4R)-1-((4-acetamidophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.1	>10	27.64364
378	N-((2S,4S)-1-((4-acetamidophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.2	0.57713	2.74476
379	5-cyclopropyl-N-((2S,4R)-2-methyl-1-(phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	390	3.35227	
380	N-((2S,4R)-1-((3-cyanophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(437.15)	0.32325	
381	5-cyclopropyl-N-((2S,4S)-1-((6-(isobutyl(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	476.3	>10	>40
382	N-((3R,4R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-(hydroxymethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	391.1	2.54424	

383	5-cyclopropyl-N-((3R,4R)-3-(hydroxymethyl)-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)isoxazole-3-carboxamide	391.4	3.02223	
384	N-((2S,4R)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-(hydroxymethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	391.1	4.03559	
385	N-((3S,4S)-1-((3-aminopropyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371	0.08821	1.22936
386	N-((3S,4R)-1-((3-aminopropyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371	0.02816	0.33952
387	N-((3R,4S)-1-((3-aminopropyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.15	0.07	0.78774
388	N-((3R,4R)-1-((3-aminopropyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371.2	0.46245	
389	N-((2S,4R)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	451.2	>10	
390	N-((2R,4R)-1-((3-aminopropyl)sulfonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.2	0.4637	2.97188
391	N-((2S,4S)-1-(2-(1-(aminomethyl)cyclohexyl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	403.2	5.72321	>10
392	N-((2R,4S)-1-(3-(2-aminopropan-2-yl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.1	>10	
393	5-cyclopropyl-N-((2S,4S)-1-((1-methoxypropan-2-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	386	3.15999	
394	5-cyclopropyl-N-((2S,4R)-1-((2-isopropoxyethyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	400.1	>10	
395	N-((1R,3s,5S)-8-((2-aminoethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	369.1	0.6108	3.1641
396	N-((1R,3r,5S)-8-((2-aminoethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	369.15	0.04169	0.3747

397	N-((2R,4S)-1-((4-acetamidophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.1	>10	>10
398	N-((2S,4S)-1-((3-cyanophenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	415	0.212	1.2065
399	5-cyclopropyl-N-((1R,3s,5S)-8-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	402	0.83319	2.86872
400	5-cyclopropyl-N-((1R,3r,5S)-8-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	402	4.1308	>10
401	5-cyclopropyl-N-(9-(phenylsulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	416	0.79319	2.94997
402	N-(9-((4-acetamidophenyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	473.1	4.92371	>10
403	N-((1R,3r,5S)-8-((4-acetamidophenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	458.9	10	>10
404	5-cyclopropyl-N-((1R,3s,5S)-8-((2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	459	1.40067	2.91816
405	5-cyclopropyl-N-((1R,3r,5S)-8-((2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	458.9	9.39268	>10
406	N-((2S,4R)-2-benzyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487.35	3.41263	
407	N-((2R,4R)-2-benzyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487.1	3.81295	>10
408	N-((2R,4S)-2-benzyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487.1	1.14883	
409	N-((2S,4R)-2-benzyl-1-((2-morpholinoethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	(525.3)	>10	
410	5-cyclopropyl-N-(9-((3-morpholinopropyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	467.1	6.3223	>10

411	5-cyclopropyl-N-((2S,4R)-1-((6-(isobutyl(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	476.1	>10	
412	5-cyclopropyl-N-((2S,4S)-1-((6-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	478.3	2.12299	8.22448
413	5-cyclopropyl-N-((2S,4S)-1-((6-((2-methoxyethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	464.25	1.4827	4.51041
414	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((6-(methyl(2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	533.3	0.88858	2.60848
415	N-((2S,4R)-1-((6-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	449.1	0.13482	5.61852
416	5-cyclopropyl-N-(8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide		0.16357	
417	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411	0.00307	0.0508
418	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	410.95	0.01717	0.19706
419	N-((2S,4R,5S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.25	1.95467	>10
420	N-((2R,4S,5R)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	389.2	0.01132	0.20488
421	N-((3S,4S)-1-((1r,4S)-4-aminocyclohexane-1-carbonyl)-3-(hydroxymethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	391.1	2.51243	
422	N-((3R,4S)-1-((1r,4R)-4-aminocyclohexane-1-carbonyl)-3-(hydroxymethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	391.1	1.9415	

423	N-((2R,4S)-1-((3-aminopropyl)sulfonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.2	0.25029	1.85554
424	N-((2S,4S)-1-((3-aminopropyl)sulfonyl)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447.2	0.22763	1.80492
425	N-((2R,4S)-1-(1H-benzo[d]imidazole-5-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	394	>10	
426	N-((2S,4R)-1-(1H-benzo[d]imidazole-5-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	394	>10	
427	N-(1-(2-(1H-imidazol-2-yl)acetyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	358.1	>10	>10
428	N-((2R,4R)-1-((1H-imidazol-4-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	380	0.73212	2.58364
429	N-((1R,3R,5S)-8-((1s,4S)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	387.1	0.35096	
430	N-((1R,3s,5S)-8-((4-acetamidophenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	459.2	3.65777	4.51957
431	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isonicotinamido)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	522.25	>10	>10
432	N-((1R,3r,5S)-8-((6-chloro-2-oxoindolin-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	491.15	6.29941	>10
433	5-cyclopropyl-N-((1R,3r,5S)-8-((2-oxoindolin-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	457	4.19179	>10
434	5-cyclopropyl-N-((1R,3r,5S)-8-((2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	458	2.40802	>10
435	5-cyclopropyl-N-((1R,3s,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.2	2.00184	5.58678
436	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.2	0.0613	0.28517

437	N-((2S,4S)-2-benzyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487.1	1.00347	4.62346
438	N-((2S,4R)-2-benzyl-1-((3-morpholinopropyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	517.35	9.17764	>10
439	N-((2R,4R)-2-benzyl-1-((3-morpholinopropyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	517.35	>10	>10
440	5-cyclopropyl-N-((1R,3s,5S)-8-((2-morpholinoethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	439.2	>10	>10
441	5-cyclopropyl-N-((1R,3r,5S)-8-((2-morpholinoethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	439.25	1.61126	3.67271
442	5-cyclopropyl-N-(9-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	437.1	1.11218	4.5508
443	5-cyclopropyl-N-(9-((2-morpholinoethyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	453	>10	>10
444	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-(methylamino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	385	0.01309	0.18073
445	N-(5-((3-aminopropyl)sulfonyl)-5-azaspiro[3.5]nonan-8-yl)-5-cyclopropylisoxazole-3-carboxamide	397	0.13047	
446	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((6-(methylamino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	420.2	0.89031	2.25375
447	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((6-(methylamino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	420	>10	
448	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((6-(methylamino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	420.1	>10	
449	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((6-(methylamino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	420	>10	>10

450	5-cyclopropyl-N-((2S,4S)-1-((6-(isobutylamino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	462.1	1.09589	3.47813
451	5-cyclopropyl-N-((2R,4S)-1-((6-(isobutylamino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	462.1	>10	
452	5-cyclopropyl-N-((2S,4R)-1-((6-(isobutylamino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	462.1	>10	
453	5-cyclopropyl-N-((2R,4R)-1-((6-(isobutylamino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	462.1	7.19308	>10
454	5-cyclopropyl-N-((2R,4R)-1-((6-(isobutyl(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	476.3	>10	>10
455	5-cyclopropyl-N-((2R,4R)-1-((6-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	478.25	>10	>10
456	5-cyclopropyl-N-((2R,4S)-1-((6-((2-methoxyethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	464	>10	
457	5-cyclopropyl-N-((2R,4R)-1-((6-((2-methoxyethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	464.25	>10	>10
458	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((6-((2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	519.3	0.13177	0.58095
459	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((6-((2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	519.35	2.35941	4.57896
460	5-cyclopropyl-N-((2R,4R)-2-methyl-1-((6-(methyl(2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	533.3	>10	>10
461	N-((2S,4S)-1-((6-((2-aminoethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463.25	0.01418	3.85496

462	N-((2S,4R)-1-((6-((2-aminoethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463.3	0.3055	
463	N-((2R,4R)-1-((6-((2-aminoethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463	0.16261	4.33037
464	N-((2R,4R)-1-((6-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	449.25	0.08973	3.30448
465	5-cyclopropyl-N-(9-((6-(isobutylamino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	488.1	3.11956	6.16422
466	N-((2S,4S)-1-((5-chloropyridin-2-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	424.9	0.12114	
467	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2-(methylamino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	420.3	3.73627	5.75977
468	methyl 1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-4-(5-cyclopropylisoxazole-3-carboxamido)-5-methylpiperidine-3-carboxylate	433.2	1.22465	
469	N-(1-((1r,4r)-4-aminocyclohexane-1-carbonyl)-3-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	437.2	6.27588	
470	N-(1-((3-aminopropyl)sulfonyl)-3-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	433.1	2.7581	
471	methyl 1-(4-aminobutanoyl)-4-(5-cyclopropylisoxazole-3-carboxamido)-5-methylpiperidine-3-carboxylate	393.1	5.75922	
472	5-cyclopropyl-N-(9-((2-(isobutyl(methyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	502.2	>10	
473	5-cyclopropyl-N-(9-((2-(isobutylamino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	488.1	5.97434	
474	5-cyclopropyl-N-((2S,4S)-1-((2-(isobutylamino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	462.2	2.73729	

475	N-((2S,4S)-1-((2-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	449	0.08652	1.34483
476	N-(9-((2-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	475	1.30942	
477	N-((2S,4S)-1-((3-carbamoylphenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	433.2	0.93164	3.26041
478	N-((2S,4S)-1-(4-benzylpiperazine-1-carbonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	452.3	>10	>10
479	N-((2R,4R)-1-(4-(1-aminocyclobutyl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	424.1	0.28891	2.02944
480	N-((2R)-1-((3-aminopropyl)sulfonyl)-2-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	433.1	0.06583	2.23715
481	N-((2S)-1-((3-aminopropyl)sulfonyl)-2-phenylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	433.1	0.47891	4.47317
482	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((tetrahydrofuran-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	384	0.92833	2.83154
483	N-((2S,4S)-1-((1H-imidazol-4-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	380	0.53253	2.12754
484	N-((1R,3s,5S)-8-((3-aminopropyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	383.15	0.0792	1.44334
485	N-((1R,3r,5S)-8-((3-aminopropyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	383.2	0.00507	0.12898
486	N-((1R,3S,5S)-8-((1s,4S)-4-aminocyclohexane-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	387.2	>10	
487	5-cyclopropyl-N-((1R,3r,5S)-8-(pyrrolidin-3-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	395		

488	5-cyclopropyl-N-(9-((piperidin-3-ylmethyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	437.1	0.04505	0.85719
489	5-cyclopropyl-N-((1R,3s,5S)-8-((4-(isonicotinamido)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	522.1	5.41877	6.66386
490	N-((1R,3s,5S)-8-((6-chloro-2-oxoindolin-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	491.15	9.23127	>10
491	N-((1R,3s,5S)-8-((5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	493.15	>10	>10
492	N-((1R,3r,5S)-8-((5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	493.15	>10	
493	5-cyclopropyl-N-((1R,3s,5S)-8-((2-oxoindolin-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	457	0.84167	2.74654
494	5-cyclopropyl-N-((1R,3s,5S)-8-((2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	458		5.18222
495	5-cyclopropyl-N-((1R,3s,5S)-8-((3-morpholinopropyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	453.25	>10	>10
496	5-cyclopropyl-N-((1R,3r,5S)-8-((3-morpholinopropyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	453.25	0.16199	0.85436
497	N-((2S,4S)-2-benzyl-1-((3-morpholinopropyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	517.35	>10	>10
498	N-((2R,4S)-2-benzyl-1-((3-morpholinopropyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	517.35	9.95967	>10
499	N-((2R,4S)-2-benzyl-1-((2-morpholinoethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	503.1	>10	>10
500	N-((2S,4S)-1-((3-(benzylamino)propyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	461.1	0.00813	0.10571

501	N-((2R,4S)-1-((3-aminopropyl)sulfonyl)-2-isopropylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	399.1		4.48798
502	N-((2S,4R)-1-((3-aminopropyl)sulfonyl)-2-isopropylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	399.1	0.76582	>10
503	N-((2R,4R)-1-((3-aminopropyl)sulfonyl)-2-isopropylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	399.1	1.06393	>10
504	5-cyclopropyl-N-((2R,4S)-1-((6-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	478.1	>10	>10
505	5-cyclopropyl-N-((2S,4R)-1-((6-((2-methoxyethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	464	>10	>10
506	5-cyclopropyl-N-((2R,4S)-2-methyl-1-((6-((2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	519.35	3.96727	>10
507	5-cyclopropyl-N-((2S,4R)-2-methyl-1-((6-((2-morpholinoethyl)amino)pyridin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	519.35	5.54025	>10
508	N-((2R,4S)-1-((6-((2-aminoethyl)(methyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463	0.31958	
509	N-((2S,4S)-1-((6-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	449.1	0.00592	
510	5-cyclopropyl-N-((2S,4S)-1-((2-(isobutyl(methyl)amino)pyridin-4-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	476.3	>10	
511	5-cyclopropyl-N-((2S,4R)-1-((2-(isobutyl(methyl)amino)pyridin-4-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	476.3	>10	
512	N-((2R,4S)-1-((2-((2-aminoethyl)(methyl)amino)pyridin-4-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463.25	0.4872	
513	N-((2S,4S)-1-((6-cyanopyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	416.1	1.09324	

514	5-cyclopropyl-N-(9-((6-(isobutyl(methyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	502.2	>10	
515	N-(9-((6-((2-aminoethyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	475.2	0.01762	
516	N-(9-((6-((3-aminopropyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	489.1	0.07423	
517	N-(9-((6-((3-aminopropyl)(methyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	503.2	0.08028	
518	5-cyclopropyl-N-((2S,4S)-1-(N,N-diethylsulfamoyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	385.1	3.7176	
519	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((6-(trifluoromethyl)pyridin-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide		0.20407	
520	N-((2S,4S)-1-((6-((3-aminopropyl)amino)pyridin-2-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	463.25	0.05007	
521	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((6-(methyl(2-morpholinoethyl)amino)pyridin-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	533.2	4.50489	
522	N-((2S,4S)-1-((6-aminopyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	406	0.40714	
523	N-((2S,4S)-1-((2-aminopyridin-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	406	1.0836	
524	5-cyclopropyl-N-(9-((2-(methylamino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	446.2	1.84758	
525	N-((1R,3r,5S)-8-((4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	423.3	0.0008	0.009
526	5-cyclopropyl-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.25	0.001	0.015

527	5-cyclopropyl-N-((1R,3r,5S)-8-(piperazin-1-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	410.0	0.003	0.032

* IC_{50} values are an average of n=1 to n=50

Table 2A

Cpd. No.	Chemical Name	LCMS M+H or (M+Na)	SMYD3 Biochem IC_{50} (μM)*	SMYD3 Cell IC_{50} (μM)*
528	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	533	0.0006	0.0231
529	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	412	0.0008	0.0152
530	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1-phenethylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	515.1	0.0009	0.0239
531	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(2-hydroxyethyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	467	0.0009	0.0331
532	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	424	0.0009	0.0214
533	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.0010	0.0308
534	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(3-hydroxypropyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	481	0.0011	0.0277
535	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(methylamino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.0012	0.0212
536	N-((1R,3r,5S)-8-(((1-benzylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	513	0.0012	0.0580

537	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(((1-phenethylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	515.05	0.0013	0.0725
538	5-cyclopropyl-N-((2S,4S)-1-(((1-(2-hydroxyethyl)piperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	455	0.0013	0.0294
539	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	423.05	0.0013	0.0134
540	N-((1R,3R,5S)-8-(((1s,4S)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	423	0.0013	0.0152
541	N-((2S,4S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447	0.0014	0.0259
542	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(3-methoxypropyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	495	0.0016	0.0496
543	5-cyclopropyl-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.2	0.0018	0.0445
544	N-((2S,4S)-1-(((1-benzylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	501.1	0.0019	0.0447
545	5-cyclopropyl-N-((2S,4S)-1-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	440	0.0020	0.0399
546	N-((2S,4S)-1-((4-(benzylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.0021	0.0360
547	5-cyclopropyl-N-((1R,3r,5S)-8-((piperidin-3-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.3	0.0023	0.0704
548	N-((2S,4S)-1-((4-aminobutyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	385	0.0024	0.0941

549	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(2-(piperidin-1-yl)ethyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	534	0.0025	0.3124
550	5-cyclopropyl-N-((2S,4S)-1-(((1-isopropylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	453.05	0.0026	0.1685
551	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(3,3,3-trifluoropropyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	519	0.0029	0.0542
552	N-((1R,3r,5S)-8-((6-amino-2-azaspiro[3.3]heptan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	436	0.0031	0.0492
553	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1-(2-(piperidin-1-yl)ethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	522.15	0.0034	0.1059
554	5-cyclopropyl-N-((2S,4S)-1-(((1-(2-methoxyethyl)piperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	469.1	0.0035	0.0704
555	N-((2S,4S)-1-((3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	424	0.0037	0.0239
556	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(2-methoxyethyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	481	0.0039	0.0557
557	5-cyclopropyl-N-((2S,4S)-1-(((1-isobutylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	467.1	0.0042	0.2607
558	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	398.2	0.0043	0.0719
559	N-((1R,3r,5S)-8-((2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	450	0.0047	0.0319

560	5-cyclopropyl-N-((1R,3r,5S)-8-((8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	450	0.0048	0.0516
561	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(methylamino)butyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	399	0.0051	
562	5-ethyl-N-((1R,3r,5S)-8-((piperidin-4-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	411	0.0052	0.0615
563	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-(methylamino)ethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	440	0.0053	0.3386
564	N-((1R,3r,5S)-8-((3-((2-aminoethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	426	0.0053	0.1660
565	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	438	0.0060	0.0494
566	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-((4-(trifluoromethyl)benzyl)amino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	529	0.0061	0.3222
567	N-((3S,4R)-1-((4-aminopiperidin-1-yl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	412	0.0061	0.1131
568	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425.1	0.0063	0.1559
569	5-cyclopropyl-N-((1R,3R,5S)-8-((((R)-piperidin-3-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423	0.0066	0.0394
570	N-((2S,4S)-1-((2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	410	0.0067	0.0839
571	N-((1R,3r,5S)-8-((3,6-diazabicyclo[3.1.1]heptan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	422	0.0075	0.0992

572	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((S)-3-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0078	0.0536
573	N-((2R,4R)-1-(((1-benzylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	501.1	0.0080	0.2933
574	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((1-methylpiperidin-4-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411	0.0080	0.1047
575	5-cyclopropyl-N-((1R,3S,5S)-8-((((S)-piperidin-3-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423	0.0080	0.0674
576	5-cyclopropyl-N-((2S,4S)-1-((4-(dimethylamino)butyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	413	0.0081	0.1064
577	N-((2S,4S)-1-((2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	424	0.0092	0.1342
578	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-((naphthalen-2-ylmethyl)amino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	511	0.0094	0.2887
579	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(((1-(2-(piperidin-1-yl)ethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	522.15	0.0095	0.5871
580	N-((1R,3r,5S)-8-((2,6-diazaspiro[3.3]heptan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	422	0.0097	0.0889
581	5-cyclopropyl-N-((2S,4S)-1-((4-(isopropylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	454	0.0101	0.1429
582	5-cyclopropyl-N-((1R,3r,5S)-8-((6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	436	0.0101	0.1513
583	5-cyclopropyl-N-((2R,4R)-1-(((1-(2-methoxyethyl)piperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	469.1	0.0104	0.2343

584	5-cyclopropyl-N-((2S,4S)-1-(((S)-3-ethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.0105	0.1586
585	N-((2S,4S)-1-((1,4-diazepan-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	412	0.0106	0.1857
586	N-((1R,3r,5S)-8-((3-((2-aminoethyl)(methyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	440	0.0107	0.2627
587	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1-(2-morpholinoethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	524.1	0.0107	0.3105
588	N-((2S,4S)-1-((3,6-diazabicyclo[3.1.1]heptan-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	410	0.0108	0.1505
589	5-cyclopropyl-N-((2R,4R)-1-(((1-(2-hydroxyethyl)piperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	455	0.0109	0.1525
590	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-(dimethylamino)ethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	454	0.0109	0.1751
591	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(methylamino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	397	0.0111	0.1498
592	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	424	0.0116	0.1061
593	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(dimethylamino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	411	0.0118	0.1472
594	N-((1R,3r,5S)-8-(N-(2-azaspiro[3.3]heptan-6-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	436	0.0120	0.6692
595	5-cyclopropyl-N-((2R,4S,5R)-2,5-dimethyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0126	0.0778

596	N-((1R,3r,5S)-8-((2-((2-aminoethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	412	0.0128	0.3792
597	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(pyrrolidin-1-yl)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437	0.0129	0.2169
598	N-((1R,3r,5S)-8-((2-((2-aminoethyl)(methyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	426	0.0131	0.4308
599	5-cyclopropyl-N-((1R,3r,5S)-8-((2-((2-(dimethylamino)ethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	440	0.0135	0.2131
600	5-cyclopropyl-N-((1R,3r,5S)-8-((3,3-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438	0.0135	0.1184
601	N-((2S,4R,5S)-1-((3-aminopropyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	385	0.0143	0.3334
602	N-((1R,3r,5S)-8-((3,8-diazabicyclo[3.2.1]octan-8-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	436	0.0145	0.1319
603	5-cyclopropyl-N-((1R,3r,5S)-8-((2-((2-(dimethylamino)ethyl)(methyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	454	0.0147	0.2390
604	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-methoxyethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	441	0.0162	0.1999
605	5-cyclopropyl-N-((1R,3r,5S)-8-((2-((2-(methylamino)ethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	426	0.0175	0.3023
606	5-cyclopropyl-N-((1R,3r,5S)-8-(N-methyl-N-(1-methylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452	0.0177	0.2351
607	5-cyclopropyl-N-((2R,4R)-1-(((1-isopropylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	453.05	0.0178	1.1728

608	5-cyclopropyl-N-((3S,4R)-1-(((1-(3-hydroxypropyl)piperidin-4-yl)methyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	469	0.0178	0.2246
609	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-((3-(trifluoromethyl)benzyl)amino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	529	0.0188	0.4514
610	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-(dimethylamino)ethyl)(methyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	468	0.0194	0.3325
611	5-cyclopropyl-N-((2R,4R)-1-(((1-isobutylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	467.1	0.0200	1.0292
612	N-((2S,4S)-1-((3-((cyclohexylmethyl)amino)propyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	467	0.0207	0.2172
613	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	521	0.0209	0.2124
614	N-((3S,4R)-1-((4-(benzylamino)piperidin-1-yl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.0212	0.3043
615	N-((2S,4S)-1-((3,8-diazabicyclo[3.2.1]octan-8-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	424	0.0217	0.2333
616	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(4-(piperidin-3-yl)benzoyl)piperidin-4-yl)isoxazole-3-carboxamide	437	0.0219	0.5949
617	5-cyclopropyl-N-((2S,4S)-1-((4-ethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.0228	0.1832
618	5-cyclopropyl-N-((3S,4R)-3-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411	0.0232	0.2196
619	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(2-morpholinoethyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	536	0.0232	0.5921

620	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(methyl(2-(methylamino)ethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	440	0.0233	0.3392
621	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	398	0.0234	0.2226
622	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(methyl(2-(methylamino)ethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	454	0.0234	0.4635
623	5-cyclopropyl-N-((3S,4R)-1-(((1-(2-hydroxyethyl)piperidin-4-yl)methyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	455	0.0237	0.2310
624	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((S)-2-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0246	0.2837
625	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.0253	0.2236
626	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	424	0.0253	0.1569
627	N-((3S,4R)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447	0.0265	0.2431
628	N-((2S,4R,5S)-1-((3-(benzylamino)propyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	475	0.0273	0.5767
629	5-cyclopropyl-N-((2R,4S,5R)-2,5-dimethyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.0282	0.4070
630	5-cyclopropyl-N-((2S,4S)-1-((3-((cyclopropylmethyl)amino)propyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	425	0.0294	0.3965
631	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	438	0.0298	0.2985

632	5-cyclopropyl-N-((2S,4R,5S)-2,5-dimethyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.0304	0.2286
633	5-cyclopropyl-N-((2S,4S)-1-((3-(isopropylamino)propyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	413	0.0304	0.2912
634	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((R)-3-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0318	0.1755
635	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-(neopentylamino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	441	0.0325	0.3179
636	5-cyclopropyl-N-((1R,3r,5S)-8-((3-ethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438	0.0332	0.3652
637	5-cyclopropyl-N-((2S,4R,5S)-2,5-dimethyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0334	0.2032
638	5-cyclopropyl-N-((2S,4S)-1-((3,3-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.0337	0.2535
639	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-methyl-1,4-diazepan-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.0348	0.2575
640	5-cyclopropyl-N-((2S,4S)-1-((3-(isobutylamino)propyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	427	0.0357	0.4801
641	5-cyclopropyl-N-((1R,3r,5S)-8-((4-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	424	0.0363	0.1881
642	N-((2R,4S,5R)-1-((3-aminopropyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	385	0.0376	0.5708
643	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(hydroxymethyl)piperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	440	0.0378	0.2106

644	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(4-(piperidin-4-yl)benzoyl)piperidin-4-yl)isoxazole-3-carboxamide	437	0.0413	0.3031
645	N-((2S,4S)-1-((3-(benzhydrylamino)propyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	537	0.0444	0.5754
646	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0452	0.7547
647	N-((2S,4S)-2-benzyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487	0.0455	0.8087
648	5-cyclopropyl-N-((3S,4R)-1-(((1-(3-methoxypropyl)piperidin-4-yl)methyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	483	0.0468	0.3307
649	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(methylamino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	383	0.0472	0.2614
650	N-((2S,4S)-1-(N-(2-aminoethyl)sulfamoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide		0.0491	4.6303
651	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(3-(dimethylamino)pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	466	0.0506	0.5325
652	5-cyclopropyl-N-((2R,4S)-2-methyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	398	0.0511	0.3391
653	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(N-methyl-N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.0550	0.3278
654	5-cyclopropyl-N-((3S,4R)-1-(((1-(2-methoxyethyl)piperidin-4-yl)methyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	469	0.0560	0.3397
655	N-((3S,4R)-1-(((1-benzylpiperidin-4-yl)methyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	501	0.0564	0.4969
656	5-cyclopropyl-N-((1R,3r,5S)-8-((3,3,4-trimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452	0.0598	0.4406

657	N-((2R,4S,5R)-1-(4-(2-aminopropan-2-yl)benzoyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425	0.0634	0.6340
658	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(4-(piperazin-1-ylmethyl)benzoyl)piperidin-4-yl)isoxazole-3-carboxamide	452	0.0647	1.3988
659	N-((1R,3r,5S)-8-(N-(1-benzylpiperidin-4-yl)-N-methylsulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	528	0.0664	0.5776
660	5-cyclopropyl-N-((1R,3r,5S)-8-((3,4-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438	0.0667	0.4140
661	5-cyclopropyl-N-((2S,4S)-1-(((2S,5R)-2,5-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.0773	0.4903
662	N-((2S,4S)-2-benzyl-1-(((1-(2-hydroxyethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	531	0.0801	1.5480
663	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(3-(piperidin-1-yl)pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	506	0.0851	0.6705
664	N-((2R,4R)-1-(4-((R)-1-aminoethyl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397	0.0866	1.0654
665	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-methoxyethyl)(methyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	455	0.0868	
666	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((R)-2-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.0906	0.8014
667	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(N-(1-methylpiperidin-4-yl)sulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.0969	0.7306
668	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(N-methyl-N-(1-methylpiperidin-4-yl)sulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	440	0.1009	0.5763

669	5-cyclopropyl-N-((2S,4S)-1-(((R)-3,4-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.1020	0.3984
670	5-cyclopropyl-N-((1R,3r,5S)-8-((3-((2-morpholinoethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496	0.1027	0.8858
671	N-((2R,4R)-1-(4-(2-aminoethoxy)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	413	0.1035	5.5778
672	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(dimethylamino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	397	0.1043	0.3883
673	5-cyclopropyl-N-((1R,3r,5S)-9-((piperidin-4-ylmethyl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	437	0.1061	1.6774
674	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(N-methyl-N-(1-methylpiperidin-4-yl)sulfamoyl)piperidin-4-yl)isoxazole-3-carboxamide	440	0.1083	1.0760
675	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(4-((methylamino)methyl)benzoyl)piperidin-4-yl)isoxazole-3-carboxamide	397	0.1105	1.3732
676	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(((1-(2-morpholinoethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	524.15	0.1112	>10.0000
677	N-((2S,4S)-1-(N-(2-aminoethyl)-N-methylsulfamoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	386	0.1112	5.3131
678	5-cyclopropyl-N-((1R,3r,5S)-9-(N-methyl-N-(piperidin-4-yl)sulfamoyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	452	0.1131	2.6583
679	N-((2R,4R)-1-(4-((S)-1-aminoethyl)benzoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	397	0.1132	1.2977
680	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3,3,4-trimethylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	440	0.1187	0.5921
681	N-((2R,4S,5R)-1-((3-(benzylamino)propyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	474	0.1195	0.9296

682	N-((2S,4S)-2-benzyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	501	0.1211	1.2477
683	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(6-(piperazin-1-yl)nicotinoyl)piperidin-4-yl)isoxazole-3-carboxamide	439	0.1217	1.7798
684	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(hydroxymethyl)-4-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	454	0.1225	0.9230
685	5-cyclopropyl-N-((2R,4S,5R)-2,5-dimethyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.1244	0.2542
686	5-cyclopropyl-N-((2R,4R)-1-(4-((dimethylamino)methyl)benzoyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	411	0.1289	1.5414
687	5-cyclopropyl-N-((1R,3s,5S)-9-(N-methyl-N-(piperidin-4-yl)sulfamoyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	452	0.1302	1.7075
688	N-((2R,4S,5R)-1-((2-aminoethyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371	0.1306	0.7834
689	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(2-methylpyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437	0.1307	0.7636
690	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(3-hydroxypyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	439	0.1376	0.5532
691	N-((2R,4S)-2-benzyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487	0.1440	1.9453
692	5-cyclopropyl-N-((1R,3r,5S)-8-((3,5-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438	0.1482	0.6374
693	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1-(2-(piperidin-1-yl)ethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	522	0.1556	4.0418

694	N-((2S,4R,5S)-1-((2-aminoethyl)sulfonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	371	0.1570	0.9523
695	N-((2S,4S)-1-((3-amino-1-phenylpropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447	0.1686	1.8333
696	N-((3S,4R)-1-(N-(1-benzylpiperidin-4-yl)sulfamoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.1703	1.5473
697	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((3-(phenylamino)propyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	447	0.1777	1.5607
698	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1-(3,3,3-trifluoropropyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	507	0.1790	0.7457
699	5-cyclopropyl-N-((2S,4S)-1-((3,4-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.1930	0.6578
700	N-((2S,4S)-2-benzyl-1-((piperidin-3-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487	0.1936	2.1088
701	5-cyclopropyl-N-((2S,4S)-1-((3,5-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.2103	1.8410
702	5-cyclopropyl-N-((1R,3r,5S)-8-((3,4,5-trimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452	0.2151	1.2352
703	5-cyclopropyl-N-((1R,3r,5S)-8-((3-(methyl(2-morpholinoethyl)amino)propyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	510	0.2170	0.8042
704	N-((2R,4S)-1-((3-amino-1-phenylpropyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	447	0.2181	
705	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(phenethylamino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	473	0.2250	1.5149
706	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(pyridin-4-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	391	0.2376	1.2126

707	N-((2S,4S)-2-benzyl-1-(((1-(3-hydroxypropyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	545	0.2469	2.5353
708	N-((2S,4S)-1-((6-aminopyridin-2-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	406	0.2521	1.6621
709	5-cyclopropyl-N-((1R,5R)-9-(N-methyl-N-(1-methylpiperidin-4-yl)sulfamoyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	466	0.2575	1.9155
710	5-cyclopropyl-N-((3S,4R)-3-methyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	412	0.2607	0.8310
711	5-cyclopropyl-N-((2S,4S)-1-(((R)-3-ethyl-4-methylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	440	0.2725	1.1521
712	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((2S,5R)-2,4,5-trimethylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	440	0.2749	1.0984
713	5-cyclopropyl-N-((1R,3r,5S)-8-((3-ethyl-4-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452	0.2934	1.1757
714	N-((2S,4R)-2-benzyl-1-(N-methyl-N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.2949	3.1527
715	N-((2R,4S)-2-benzyl-1-(N-methyl-N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.2971	3.0425
716	N-((2R,4R)-1-((3-amino-4-phenylbutyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	461	0.3027	3.5340
717	N-((2S,4S)-2-benzyl-1-(pyrrolidin-3-ylsulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	459	0.3061	2.0240
718	5-cyclopropyl-N-((1R,3s,5S)-9-(N-methyl-N-(1-methylpiperidin-4-yl)sulfamoyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	466	0.3090	1.6220
719	N-((3S,4R)-1-(N-(1-benzylpiperidin-4-yl)-N-methylsulfamoyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	516	0.3199	1.2054

720	N-((2S,4S)-2-benzyl-1-(((1-(2-methoxyethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	545	0.3218	2.4270
721	5-cyclopropyl-N-((1R,3s,5S)-8-((piperidin-3-ylmethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423	0.3224	1.8253
722	5-cyclopropyl-N-((1R,3r,5S)-8-((3-phenylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	486	0.3257	1.5226
723	N-((2S,4R)-2-benzyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487	0.3260	2.7313
724	5-cyclopropyl-N-((1R,3s,5S)-8-(N-methyl-N-(piperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438	0.3330	2.4407
725	N-((2S,4S)-2-benzyl-1-(piperidin-3-ylsulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	473	0.3401	3.0662
726	N-((1R,3r,5S)-8-((2-(3-(benzyloxy)pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	529	0.3596	2.4667
727	(E)-5-cyclopropyl-N-(1-((3-(methylamino)prop-1-en-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	369	0.3633	1.3883
728	5-cyclopropyl-N-((2S,4S)-1-(((R)-3-isopropyl-4-methylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	454	0.3805	1.3655
729	5-cyclopropyl-N-((1R,3s,5S)-8-(piperidin-3-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	409	0.4110	2.5264
730	N-((1R,3r,5S)-9-((2-aminopyridin-4-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	432	0.4128	1.3188
731	5-cyclopropyl-N-((2S,4R,5S)-2,5-dimethyl-1-((4-methylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	426	0.4183	1.3321
732	5-cyclopropyl-N-((2S,4R,5S)-2,5-dimethyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.4313	1.4616

733	N-((1R,5R)-9-((5-chloropyridin-2-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	451	0.4417	1.9585
734	N-((1R,3r,5S)-9-((2-((3-aminopropyl)amino)pyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	489	0.4425	4.1727
735	5-cyclopropyl-N-((2S,4S)-1-(((S)-3,4-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426	0.4458	1.3552
736	N-((2S,4S)-1-((3-benzylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	488	0.4521	2.0254
737	N-((2S,4S)-1-((2-benzylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	488	0.4692	6.9424
738	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1-(2-morpholinoethyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	524	0.4765	2.8209
739	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(pyridin-4-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	431	0.4911	2.3968
740	N-((1R,3s,5S)-9-((6-aminopyridin-2-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	432	0.4976	
741	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-methylpyridin-2-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	405	0.5123	
742	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(methyl(2-morpholinoethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496	0.5129	0.8991
743	5-cyclopropyl-N-((1R,3r,5S)-8-((2-((2-morpholinoethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	482	0.5137	1.8184
744	N-((2R,4R)-2-benzyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	487	0.5179	2.3476
745	N-((2S,4S)-2-benzyl-1-((pyrrolidin-2-ylmethyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	473	0.5333	2.6361

746	5-cyclopropyl-N-((2R,4S,5R)-2,5-dimethyl-1-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425	0.5406	1.6619
747	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(1-methyl-1H-benzo[d]imidazole-5-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	408	0.5828	2.4138
748	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(methyl(phenethyl)amino)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	487	0.5844	3.1758
749	N-((1R,3r,5S)-8-((3-benzylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	500	0.5903	3.5562
750	N-((2S,4S)-2-benzyl-1-(((1-(3-methoxypropyl)piperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	559	0.6247	3.4693
751	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((R)-3-phenylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	474	0.6332	2.8860
752	N-((2R,4R)-2-benzyl-1-(pyrrolidin-3-ylsulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	459	0.6667	2.4929
753	5-cyclopropyl-N-((1R,3s,5S)-9-((5-fluoropyridin-3-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	435	0.6723	2.0403
754	N-((2S,4S)-1-(N-(2-chloro-6-fluorobenzyl)sulfamoyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	471	0.6757	3.7071
755	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((3S,5R)-3,4,5-trimethylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	440	0.6773	2.3828
756	N-((2S,4S)-1-((2-aminopyridin-4-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	406	0.6839	1.7689
757	N-((2R,4R)-2-benzyl-1-(N-methyl-N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	502	0.7255	7.6085
758	N-((1R,3r,5S)-8-((3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	452	0.7306	1.6477

759	5-cyclopropyl-N-((2S,4S)-1-(((R)-3-(2-hydroxyethyl)-4-methylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	456	0.7327	2.0633
760	5-cyclopropyl-N-(1-(4-methylpiperidine-4-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide	361	0.7416	
761	N-((2S,4S)-1-((4-(acetamidomethyl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	461	0.7514	2.8538
762	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(2-(methoxymethyl)pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	467	0.7698	2.0670
763	5-cyclopropyl-N-((1R,3S)-9-((5-methylpyridin-2-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	431	0.7704	
764	5-cyclopropyl-N-((2R,4R)-2-methyl-1-(4-(2-(piperazin-1-yl)ethoxy)benzoyl)piperidin-4-yl)isoxazole-3-carboxamide	482	0.8061	9.6655
765	5-cyclopropyl-N-((1R,5R)-9-((4-ethylpiperazin-1-yl)sulfonyl)-9-azabicyclo[3.3.1]nonan-3-yl)isoxazole-3-carboxamide	452	0.8362	2.4208
766	N-((1R,3r,5S)-8-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	(481)		

* IC_{50} values are an average of n=1 to n=50

Table 3A

Cpd. No.	Chemical Name	LCMS M+H or (M+Na)	SMYD3 Biochem IC_{50}* (uM)	SMYD3 Cell IC_{50}* (uM)
767	5-cyclopropyl-N-((1R,3R,5S)-8-(((1s,4S)-4-((2-hydroxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	467.00	0.0004	0.01945
768	5-cyclopropyl-N-((1R,3R,5S)-8-(((1r,4R)-4-((2-hydroxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	467.00	0.00071	0.03468

769	5-cyclopropyl-N-((1R,3r,5S)-8-((7-phenethyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	554.00	0.00076	0.01791
770	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.00088	0.01916
771	5-cyclopropyl-N-((1R,3R,5S)-8-(((1s,4S)-4-(dimethylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.00094	0.02555
772	N-((2S,4S)-1-((((1S,3S)-3-aminocyclopentyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.00	0.00095	0.03265
773	N-((2S,4S)-1-(((1r,4S)-4-aminocyclohexyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.00	0.00103	0.01771
774	N-((2S,4S)-1-((4-amino-4-methylpiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	426.00	0.00104	0.02561
775	5-cyclopropyl-N-((2R,4R)-2-ethyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	439.00	0.00107	0.01437
776	N-((1R,3R,5S)-8-(((1r,4R)-4-(benzylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	513.00	0.00112	0.02758
777	5-cyclopropyl-N-((2R,4R)-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-2-propylpiperidin-4-yl)isoxazole-3-carboxamide	453.00	0.00114	0.01698
778	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-(4-fluorobenzyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	531.00	0.00118	0.04475
779	5-ethyl-N-((1R,3r,5S)-8-(((1-(4,4,4-trifluorobutyl)piperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	521.00	0.0012	0.02811
780	5-cyclopropyl-N-((2S,4S)-1-((4-((2-hydroxyethyl)(methyl)amino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	470.00	0.00121	0.02389

781	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-propylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	465.00	0.00122	0.02703
782	5-cyclopropyl-N-((1R,3r,5S)-8-((7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	464.00	0.00123	0.03009
783	N-((2S,4S)-1-((3-(aminomethyl)cyclopentyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.00	0.00124	0.05168
784	N-((2S,4S)-1-((((1R,3R)-3-aminocyclopentyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.00	0.00129	0.03928
785	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-ethylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.00136	0.04408
786	5-cyclopropyl-N-((1R,3R,5S)-8-(((1r,4R)-4-(methylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.00137	0.0358
787	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-isopropylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	465.00	0.00138	0.03859
788	5-ethyl-N-((1R,3R,5S)-8-(((1r,4R)-4-((2-hydroxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	455.00	0.00142	0.03076
789	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylisoxazole-3-carboxamide	411.00	0.00159	0.03186
790	N-((3S,4R)-1-(((1r,4S)-4-aminocyclohexyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	433.00	0.00181	0.056
791	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(phenethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	528.00	0.00182	0.0404
792	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-hydroxyethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	468.00	0.00185	0.04492

793	N-((2S,4S)-1-((4-aminopiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylisoxazole-3-carboxamide	400.20	0.00185	0.02625
794	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((4,4,4-trifluorobutyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	534.00	0.00187	0.03473
795	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2-((S)-1-methylpyrrolidin-3-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425.00	0.00187	0.02758
796	N-((1R,3r,5S)-8-((4-amino-4-methylpiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.0019	0.04067
797	5-ethyl-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	425.00	0.0019	0.04267
798	5-cyclopropyl-N-((1R,3R,5S)-8-(((1s,4S)-4-(methylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.00191	0.03045
799	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylisoxazole-3-carboxamide	412.00	0.00205	0.03459
800	N-((2S,4S)-1-((4-amino-3-methylpiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	426.00	0.00218	0.03972
801	N-((1R,3r,5S)-8-((6-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	422.00	0.00219	0.02773
802	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((3-(methylamino)cyclopentyl)methyl)sulfonyl) piperidin-4-yl)isoxazole-3-carboxamide	425.00	0.0023	0.02696
803	N-((1R,3r,5S)-8-((4-amino-2-methylpiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.00231	0.05897
804	N-((2S,4S)-1-((1,8-diazaspiro[4.5]decan-8-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	452.00	0.00236	0.06082
805	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452.00	0.00239	0.05324

806	N-((2S,4S)-1-((3-aminopropyl)sulfonyl)-2-propylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	399.00	0.0024	0.11318
807	5-cyclopropyl-N-((1R,3R,5S)-8-(((1r,4R)-4-(dimethylamino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.00244	0.08569
808	5-cyclopropyl-N-((2S,4S)-1-((4-((2-hydroxyethyl)amino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	456.00	0.00247	0.03681
809	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-isobutylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	479.00	0.00249	0.04268
810	N-((1R,3r,5S)-8-((4-(benzylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	514.00	0.00253	0.07225
811	N-((2S,4S)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylisoxazole-3-carboxamide	435.00	0.00258	0.03361
812	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.00265	0.04108
813	N-((2S,4S)-1-((1,7-diazaspiro[3.5]nonan-7-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.00273	0.03566
814	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2-((R)-1-methylpyrrolidin-3-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425.00	0.00277	0.04417
815	N-((1R,3R,5S)-8-(((1s,4S)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylisoxazole-3-carboxamide	411.00	0.00278	0.05262
816	5-cyclopropyl-N-((1R,3S,5S)-8-(((S)-1-(1-methylpiperidin-4-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.00291	0.05232

817	N-((1R,3r,5S)-8-((3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	436.00	0.00311	0.0348
818	5-cyclopropyl-N-((1R,3r,5S)-8-((7-isobutyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	506.00	0.00313	0.05544
819	N-((2S,4S)-1-((((1R,3R)-3-aminocyclohexyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.00	0.0032	0.12419
820	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-hydroxyethyl)(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	482.00	0.00327	0.05743
821	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isopentylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	494.00	0.00328	0.05852
822	5-cyclopropyl-N-((1R,3r,5S)-8-((8-ethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	464.00	0.00344	0.04374
823	5-cyclopropyl-N-((2S,4S)-1-(((3-(dimethylamino)cyclopentyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	439.00	0.0035	0.06716
824	N-((1R,3r,5S)-8-((7-benzyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	540.00	0.00387	0.08042
825	5-cyclopropyl-N-((1R,3R,5S)-8-(((1r,4R)-4-((2-methoxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	481.00	0.00391	0.05526
826	5-cyclopropyl-N-((1R,3R,5S)-8-(((1s,4S)-4-((2-methoxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	481.00	0.00392	0.0584
827	N-((2S,4S)-1-(((3-aminocyclohexyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.00	0.004	0.07273

828	N-((2S,4S)-1-((3,6-diazabicyclo[3.1.1]heptan-6-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	410.00	0.00418	0.14958
829	5-cyclopropyl-N-((2S,4S)-1-((4-(ethylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	440.00	0.0043	0.07016
830	N-((1R,3r,5S)-8-((4-(aminomethyl)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.00434	1.55122
831	N-((1R,3r,5S)-8-((4-amino-3-methylpiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.00436	0.08513
832	N-((1R,3r,5S)-8-((3,6-diazabicyclo[3.1.1]heptan-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	422.00	0.00438	0.13361
833	5-ethyl-N-((1R,3R,5S)-8-(((1s,4S)-4-((2-hydroxyethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	455.00	0.00447	0.07223
834	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-hydroxypropyl)(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496.00	0.00457	0.04872
835	N-((1R,3r,5S)-8-((1,8-diazaspiro[4.5]decan-8-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	464.00	0.00463	0.11781
836	N-((2S,4S)-1-((((1S,3S)-3-aminocyclohexyl)methyl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	425.00	0.00464	0.08897
837	5-cyclopropyl-N-((3S,4R)-1-(((1r,4S)-4-(dimethylamino)cyclohexyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	439.00	0.00482	0.08441
838	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(4,4,4-trifluorobutyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	548.00	0.0049	0.05236

839	N-((2S,4S)-1-((4-(benzyl(methyl)amino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	516.00	0.00497	0.15413
840	N-((1R,3r,5S)-8-((2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	422.00	0.00501	0.05595
841	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2-((S)-pyrrolidin-3-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411.00	0.00505	0.12354
842	5-cyclopropyl-N-((1R,3R,5S)-8-(((R)-1-(piperidin-4-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.0051	0.02901
843	5-cyclopropyl-N-((2S,4S)-1-((4-(isobutylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	468.00	0.00511	0.07768
844	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(phenethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	542.00	0.00528	0.30533
845	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-hydroxypropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	482.00	0.0053	0.08635
846	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isopentyl(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	508.00	0.00536	0.08024
847	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(pyrrolidin-1-yl)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	466.00	0.00553	0.07581
848	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((4-fluorobenzyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	532.00	0.00573	0.15298
849	N-((1R,3r,5S)-8-((1,7-diazaspiro[3.5]nonan-7-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	450.00	0.00595	0.06199

850	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	494.00	0.00621	0.05877
851	5-cyclopropyl-N-((2S,4S)-1-((4-((2-methoxyethyl)(methyl)amino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	484.00	0.00644	0.12457
852	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(ethyl(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	466.00	0.0065	0.1142
853	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isobutylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	480.00	0.00655	0.07104
854	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((((S)-piperidin-3-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411.00	0.00692	
855	N-((1R,3r,5S)-8-((2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	436.00	0.00706	0.06866
856	5-cyclopropyl-N-((1R,3r,5S)-8-(piperazin-1-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	410.00	0.00709	0.04668
857	5-cyclopropyl-N-((1R,3r,5S)-8-(((2,6-dimethylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.00709	0.12971
858	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((2-((R)-pyrrolidin-3-yl)ethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411.00	0.0072	0.1723
859	5-cyclopropyl-N-((1R,3R,5S)-8-(((1r,4R)-4-((2-morpholinoethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	536.00	0.00743	0.20891
860	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isobutyl(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	494.00	0.00752	0.13926

861	5-cyclopropyl-N-((2S,4S)-1-((4-((2-methoxyethyl)amino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	470.00	0.00765	0.10238
862	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(propyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	480.00	0.00769	0.07647
863	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(propylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	466.00	0.00777	0.07998
864	5-cyclopropyl-N-((1R,3r,5S)-8-((5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	436.00	0.00822	0.08622
865	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(ethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452.00	0.00855	0.09024
866	5-cyclopropyl-N-((1R,3r,5S)-8-((8-isobutyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	492.00	0.00863	0.20103
867	5-cyclopropyl-N-((1R,3r,5S)-8-((8-phenethyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	540.00	0.00867	0.84417
868	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-(pyrrolidin-1-yl)propyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	535.00	0.00868	0.31004
869	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-methoxypropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496.00	0.00905	0.11703
870	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-methoxyethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	482.00	0.00934	0.13021
871	N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-isopropylisoxazole-3-carboxamide	425.00	0.00938	0.08674

872	5-cyclopropyl-N-((2S,4S)-1-((4-(diethylamino)piperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	468.00	0.00946	0.18336
873	N-((3S,4R)-1-(((1s,4R)-4-aminocyclohexyl)sulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	411.00	0.00962	0.16925
874	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(3-(pyrrolidin-1-yl)propyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	549.00	0.00987	0.23671
875	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((((R)-piperidin-3-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411.00	0.01	
876	5-cyclopropyl-N-((1R,3R,5S)-8-(((R)-1-(1-methylpiperidin-4-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	451.00	0.01	0.18571
877	5-cyclopropyl-N-((1R,3S,5S)-8-(N-((2R,4S)-2-methylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.01002	0.17551
878	N-((1R,3R,5S)-8-(((R)-azepan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	423.00	0.01009	0.24072
879	5-isopropyl-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	439.00	0.01066	0.2063
880	N-((1R,3r,5S)-8-((4-(benzyl(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	528.00	0.01085	0.45474
881	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	480.00	0.01091	0.06886
882	5-cyclopropyl-N-((1R,3S,5S)-8-(((S)-1-(piperidin-4-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.01118	0.08563

883	N-((1R,3S,5S)-8-(((S)-azepan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	423.00	0.01204	0.12799
884	N-((1R,3S,5S)-8-(N-((2S)-2-benzylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	514.00	0.01205	0.2833
885	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1r,4S)-4-(methylamino)cyclohexyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425.00	0.01209	0.15705
886	5-cyclopropyl-N-((1R,3S,5S)-8-(N-((2S,4S)-2-methylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.01214	0.20549
887	5-cyclopropyl-N-((1R,3r,5S)-8-((3-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	424.00	0.01223	0.08778
888	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	508.00	0.01243	0.11756
889	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(diethylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	480.00	0.01269	0.2163
890	N-((2S,4S)-1-((4-amino-2-methylpiperidin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	426.00	0.01316	0.23901
891	N-((1R,3R,5S)-8-(((1R,5S)-8-amino-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	472.00	0.01331	0.14515
892	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	582.00	0.01346	0.26828
893	5-cyclopropyl-N-((1R,3r,5S)-8-(N-(1-methylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.01374	0.2392

894	5-cyclopropyl-N-((1R,3R,5S)-8-(((R)-1-(1-methylpiperidin-4-yl)-2-phenylethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	527.00	0.01388	0.27989
895	5-cyclopropyl-N-((1R,3r,5S)-8-((5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	450.00	0.01393	0.18594
896	N-((1R,3R,5S)-8-(((1r,4R)-4-amino-4-methylcyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	437.00	0.01401	0.08658
897	5-cyclopropyl-N-((1R,3r,5S)-8-(N-(piperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	424.00	0.01414	0.4229
898	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(((R)-1-phenylethyl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	516.00	0.01431	0.24039
899	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-methoxypropyl)(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	510.00	0.01448	0.16833
900	5-cyclopropyl-N-((3S,4R)-3-methyl-1-(((1s,4R)-4-(methylamino)cyclohexyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	425.00	0.01456	0.17732
901	5-cyclopropyl-N-((1R,3r,5S)-8-((2-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	424.00	0.01513	0.09768
902	5-cyclopropyl-N-((1R,3r,5S)-8-((2-ethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.01524	0.15537
903	5-cyclopropyl-N-((2S,4S)-1-(((2,6-dimethylpiperidin-4-yl)methyl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	439.00	0.0162	0.27691
904	N-((1R,3r,5S)-8-((8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	526.00	0.01688	0.39499

905	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(((S)-1-phenylethyl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	516.00	0.01713	0.33103
906	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	478.00	0.01715	0.22884
907	5-cyclopropyl-N-((1R,3r,5S)-8-((2,5-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.01774	0.23784
908	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-((2-morpholinoethyl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	525.00	0.01843	0.25328
910	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((R)-piperidin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	397.00	0.01899	0.18648
911	N-((1R,3r,5S)-8-((4-aminopiperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-isopropylisoxazole-3-carboxamide	426.00	0.02046	0.14394
912	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3-morpholinopropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	551.00	0.02093	0.31628
913	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((S)-piperidin-3-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	397.00	0.02164	0.25547
914	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(4,4,4-trifluorobutyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	546.00	0.02288	0.29876
915	5-cyclopropyl-N-((1R,3S,5S)-8-(((2S,5S)-2,5-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.02318	0.23054
916	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-methoxyethyl)(methyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496.00	0.02331	0.24735
917	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(2-(pyrrolidin-1-yl)ethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	535.00	0.02491	0.37899

918	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((3,3,3-trifluoropropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	520.00	0.02504	0.14824
919	5-cyclopropyl-N-((1R,3S,5S)-8-((((S)-piperidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.02538	0.24251
920	5-cyclopropyl-N-((1R,3R,5S)-8-(((1s,4S)-4-((2-morpholinoethyl)amino)cyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	536.00	0.02655	0.49882
921	5-cyclopropyl-N-((1R,3r,5S)-8-((2-(3-((2-hydroxyethyl)(methyl)amino)pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	496.00	0.02768	0.37264
922	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-(pyrrolidin-1-yl)ethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	521.00	0.02812	0.28224
923	5-cyclopropyl-N-((1R,3R,5S)-8-((4-(((R)-1-phenylethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	528.00	0.02856	0.3101
924	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2,6-difluorobenzyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	550.00	0.02889	0.66992
925	5-cyclopropyl-N-((1R,3r,5S)-8-((3-isopropylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452.00	0.0299	0.33958
926	5-cyclopropyl-N-((1R,3R,5S)-8-(((R)-1-methylpiperidin-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.02997	0.20921
927	5-cyclopropyl-N-((1R,3S,5S)-8-((4-(((S)-1-phenylethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	528.00	0.03088	0.40277
928	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(isopropylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	466.00	0.03621	0.51222

929	N-((1R,3r,5S)-8-((4-(aminomethyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	431.00	0.03679	10
930	5-cyclopropyl-N-((1R,3S,5S)-8-((((S)-pyrrolidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	409.00	0.03706	0.35105
931	N-((1R,3S,5S)-8-((4-((S)-1-aminoethyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	445.00	0.03725	0.52574
932	N-((2S,4S)-1-(((1R,5S,8R)-8-amino-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	438.00	0.03872	0.35112
933	5-cyclopropyl-N-((1R,3r,5S)-8-((3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	436.00	0.04243	0.09195
934	N-((1R,3R,5S)-8-((4-((R)-1-aminoethyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	445.00	0.04244	0.49372
935	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-(methyl(2-morpholinoethyl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	539.00	0.04297	0.41384
936	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(3-morpholinopropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	565.00	0.0438	0.62258
937	5-cyclopropyl-N-((2S,4S)-1-(((R)-2-ethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426.00	0.04387	0.48447
938	N-((1R,3r,5S)-8-((4-((4-cyanobenzyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	539.00	0.04409	0.50761
939	5-cyclopropyl-N-((1R,3r,5S)-8-((2-phenylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	486.00	0.04469	0.36133
940	N-((1R,3r,5S)-8-((2-benzylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	522.00	0.04752	

941	5-cyclopropyl-N-((1R,3r,5S)-8-((2,4,5-trimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452.00	0.04791	0.34078
942	N-((1R,3R,5S)-8-(N-((2R)-2-benzylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	514.00	0.04811	0.65877
943	5-cyclopropyl-N-((1R,3S,5S)-8-((4-(((S)-1-(4-fluorophenyl)ethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	546.00	0.04812	0.60158
944	5-cyclopropyl-N-((1R,3R,5S)-8-((4-(((R)-1-(4-fluorophenyl)ethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	546.00	0.04886	0.68313
945	N-((1R,3r,5S)-8-(N-benzyl-N-(piperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	514.00	0.05056	0.22262
946	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(((2-hydroxyethyl)amino)methyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	475.00	0.05097	0.33161
947	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-morpholinoethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	537.00	0.05228	0.33809
948	N-((1R,3r,5S)-8-(N-(1-benzylpiperidin-4-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	514.00	0.05241	0.41071
949	N-((2S,4S)-2-benzyl-1-(N-(piperidin-4-yl)sulfamoyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	488.00	0.05269	1.50943
950	5-cyclopropyl-N-((1R,3r,5S)-8-((2,4-dimethylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.05287	0.38988
951	5-cyclopropyl-N-((1R,3r,5S)-8-(N-methyl-N-(piperidin-3-yl)sulfamoyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	438.00	0.05415	0.39515
952	5-cyclopropyl-N-((1R,3S,5S)-8-(((S)-1-methylpiperidin-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.05621	0.28051
953	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(pyrrolidin-1-ylmethyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	485.00	0.057	0.58531

954	5-cyclopropyl-N-((2S,4S)-2-ethyl-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	439.00	0.05793	0.58254
955	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	494.00	0.05921	0.37299
956	5-cyclopropyl-N-((1R,3R,5S)-8-((((R)-pyrrolidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	409.00	0.05959	0.73276
957	5-cyclopropyl-N-((3S,4R)-1-(((1s,4R)-4-(dimethylamino)cyclohexyl)sulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide	439.00	0.06899	0.51249
958	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(pyrimidin-2-ylamino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	502.00	0.07666	0.4864
959	N-((1R,3r,5S)-8-((4-(2-aminoethyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	445.00	0.07973	10
960	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((R)-2-phenylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	474.00	0.08058	1.35436
961	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(3,3,3-trifluoropropyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	534.00	0.08159	0.36388
962	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(2-(methylamino)propan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	473.00	0.08176	0.69533
963	5-cyclopropyl-N-((1R,3r,5S)-8-((2-ethyl-4-methylpiperazin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	452.00	0.08289	0.68983
964	5-cyclopropyl-N-((1R,3R,5S)-8-((((R)-1-methylpiperidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.08296	0.44954

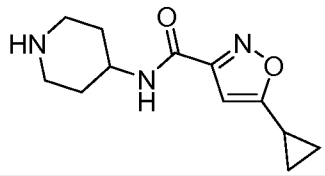
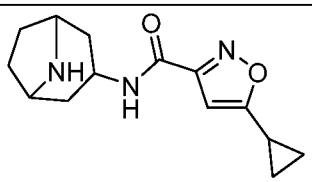
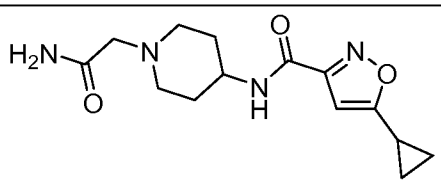
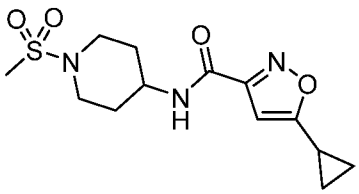
965	N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-propylisoxazole-3-carboxamide	439.00	0.08526	1.31267
966	N-((2S,4S)-2-benzyl-1-(piperazin-1-ylsulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide	474.00	0.08679	1.1965
967	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(2-morpholinoethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	549.00	0.08702	0.50309
968	N-((1R,3r,5S)-8-((4-(aminomethyl)-2-chlorophenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide	465.00	0.08835	10
969	5-cyclopropyl-N-((1R,3R,5S)-8-((((R)-1-methylpyrrolidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.08856	0.44032
970	N-((1R,3r,5S)-8-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-ethylisoxazole-3-carboxamide	469.00	0.08926	0.74846
971	5-cyclopropyl-N-((1R,3R,5S)-8-((((R)-piperidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.09085	0.46628
972	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((4-((2-phenylpropan-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	530.00	0.09327	1.27042
973	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(methyl(2-morpholinoethyl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	551.00	0.09526	1.01775
974	5-cyclopropyl-N-((2S,4S)-1-(((R)-3-ethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426.00	0.09899	0.80662
975	5-cyclopropyl-N-((2S,4S)-1-((2-isopropylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	440.00	0.10112	0.91436
976	5-cyclopropyl-N-((1R,3S,5S)-8-((((S)-1-methylpiperidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	437.00	0.10462	0.55489

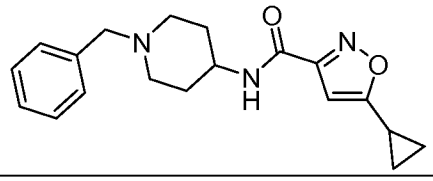
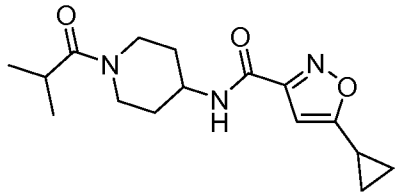
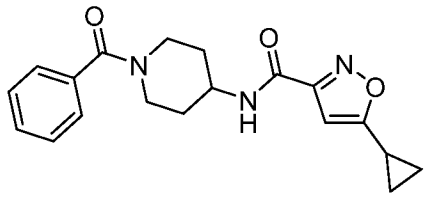
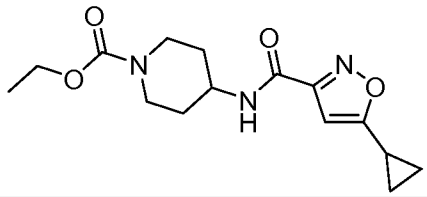
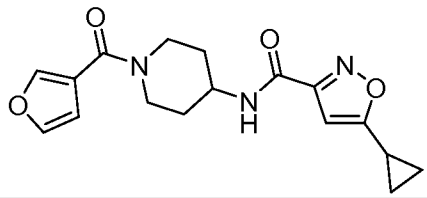
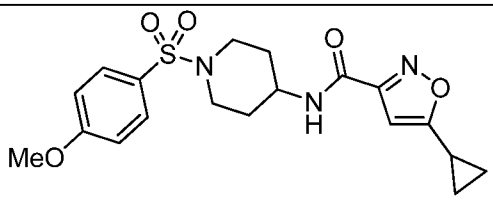
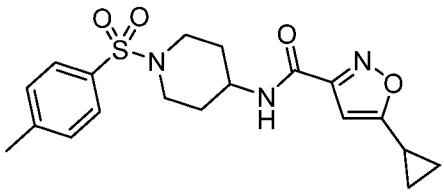
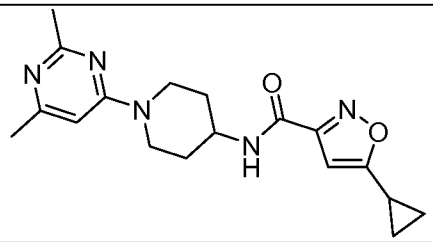
977	5-cyclopropyl-N-((1R,3r,5S)-8-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	450.00	0.10714	0.74237
978	5-cyclopropyl-N-((1R,3r,5S)-8-((4-((2-phenylpropan-2-yl)amino)piperidin-1-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	542.00	0.11701	1.32665
979	5-cyclopropyl-N-((1R,3S,5S)-8-((((S)-1-methylpyrrolidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.11891	0.43627
980	5-cyclopropyl-N-((2S,4S)-1-(((S)-2,4-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426.00	0.12021	0.69682
981	5-cyclopropyl-N-((1R,3R,5S)-8-(((R)-1-(2-hydroxyethyl)piperidin-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	453.00	0.12658	0.4656
982	5-cyclopropyl-N-((1R,3r,5S)-8-(((1-methylpyrrolidin-2-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	423.00	0.1344	0.81946
983	5-cyclopropyl-N-((2S,4S)-1-(((S)-2-ethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426.00	0.14182	0.93057
984	5-cyclopropyl-N-((2S,4S)-2-methyl-1-(((S)-2-phenylpiperazin-1-yl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	474.00	0.1419	1.84922
985	5-cyclopropyl-N-((1R,3S,5S)-8-(((S)-1-(2-hydroxyethyl)piperidin-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	453.00	0.15471	0.70778
986	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(((2-methoxyethyl)amino)methyl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	511.00	0.1556	0.80727
987	N-((2S,4R)-1-((4-(2-aminopropan-2-yl)phenyl)sulfonyl)-2-methylpiperidin-4-yl)-5-ethylisoxazole-3-carboxamide	435.00	0.15781	0.77598
988	5-cyclopropyl-N-((1R,3r,5S)-8-((4-(2-(dimethylamino)propan-2-yl)phenyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	487.00	0.15808	1.67415

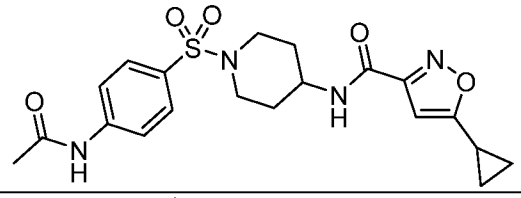
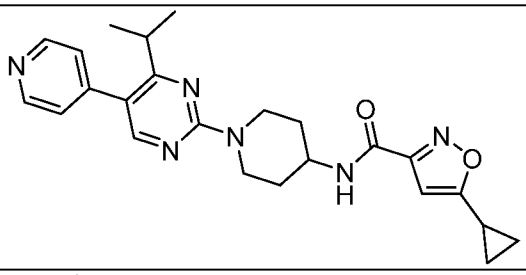
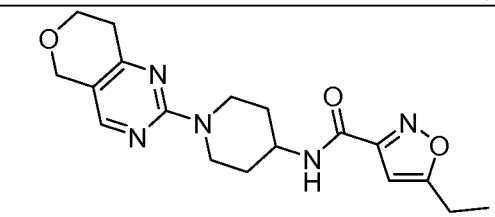
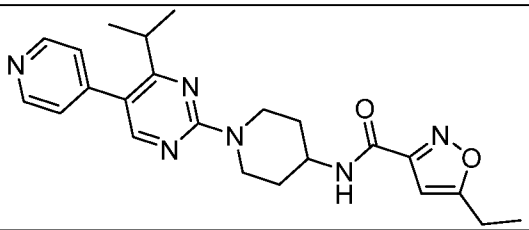
989	5-cyclopropyl-N-((2S,4S)-2-methyl-1-((piperidin-2-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide	411.00	0.17527	1.1575
990	5-cyclopropyl-N-((1R,3r,5S)-8-((8-(3,3,3-trifluoropropyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	532.00	0.18371	0.93509
991	5-cyclopropyl-N-((2S,4S)-1-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-2-propylpiperidin-4-yl)isoxazole-3-carboxamide	453.00	0.18696	2.18933
992	5-cyclopropyl-N-((2S,4S)-1-(((2S,5S)-2,5-dimethylpiperazin-1-yl)sulfonyl)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide	426.00	0.18838	1.11838
993	5-isobutyl-N-((1R,3r,5S)-8-(((1-methylpiperidin-4-yl)methyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide	453.00	0.20637	2.77149

* IC_{50} values are an average of n=1 to n=50

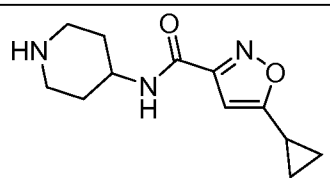
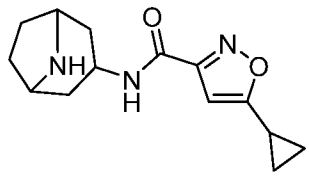
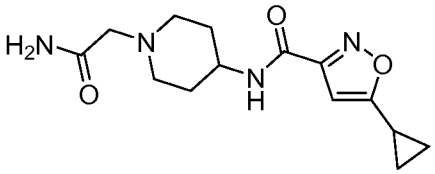
[0129] In another embodiment, a Compound of the Disclosure is a compound having Formulae **I-X**, provided that the compound is not:

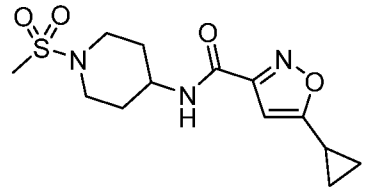
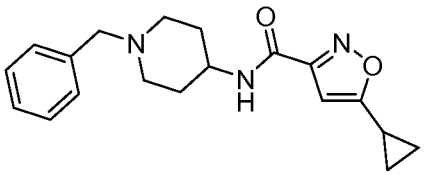
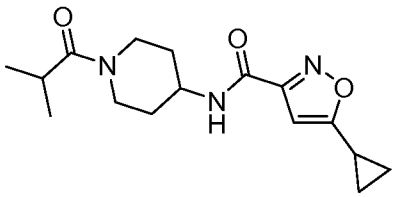
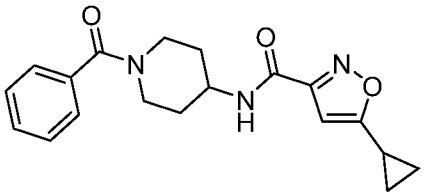
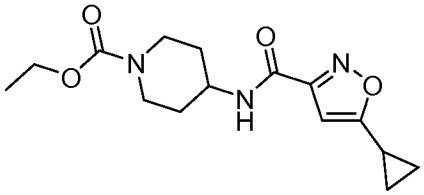
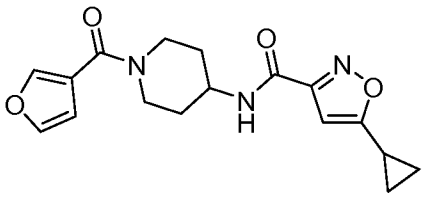
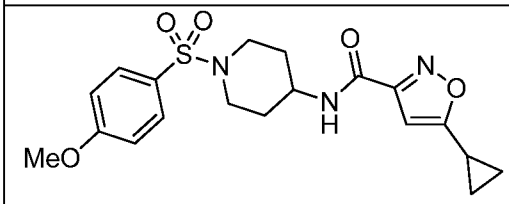
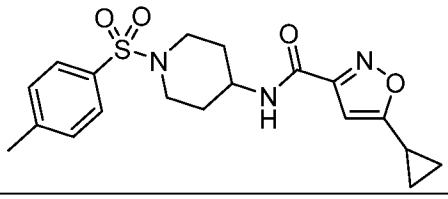
Structure	Name
	5-cyclopropyl-N-(piperidin-4-yl)isoxazole-3-carboxamide
	N-(8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide
	N-(1-(2-amino-2-oxoethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(methylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide

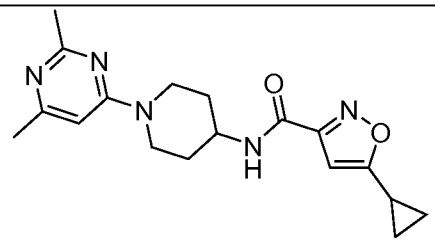
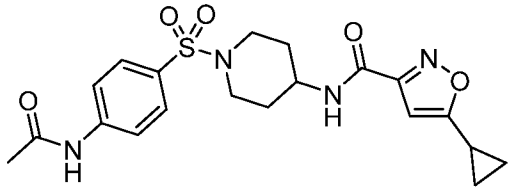
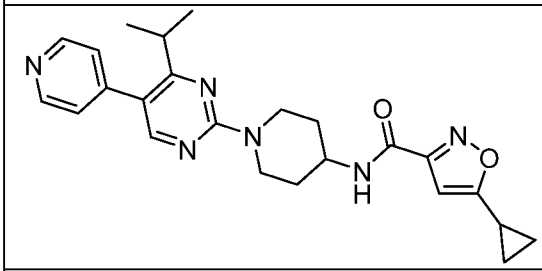
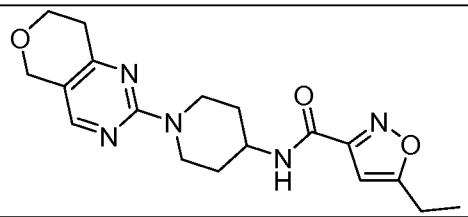
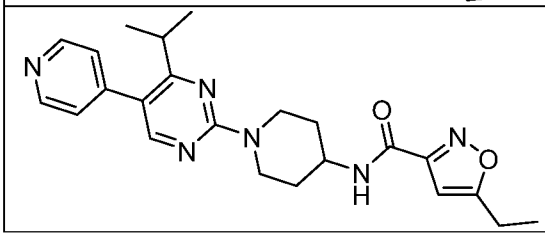
	N-(1-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-isobutyrylpiperidin-4-yl)isoxazole-3-carboxamide
	N-(1-benzoylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	ethyl 4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate
	5-cyclopropyl-N-(1-(furan-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-((4-methoxyphenyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-tosylpiperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(2,6-dimethylpyrimidin-4-yl)piperidin-4-yl)isoxazole-3-carboxamide

	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-(7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)piperidin-4-yl)-5-ethylisoxazole-3-carboxamide
	5-ethyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide

[0130] In some embodiments, the disclosure relates to pharmaceutical compositions comprising one or more of the following compounds:

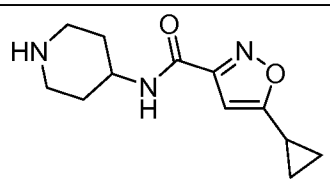
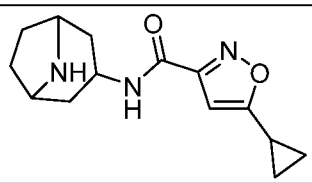
Structure	Name
	5-cyclopropyl-N-(piperidin-4-yl)isoxazole-3-carboxamide
	N-(8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide
	N-(1-(2-amino-2-oxoethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide

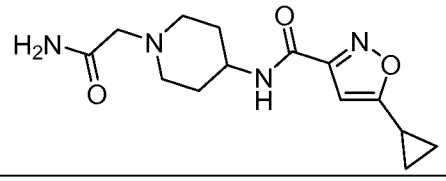
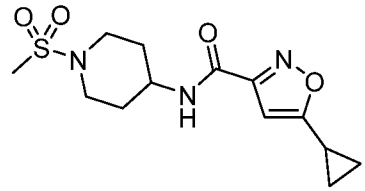
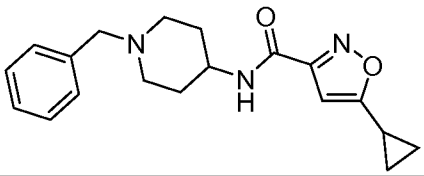
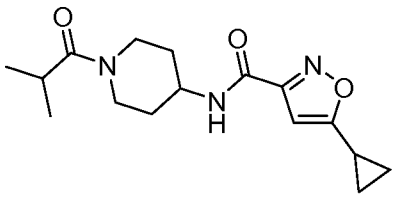
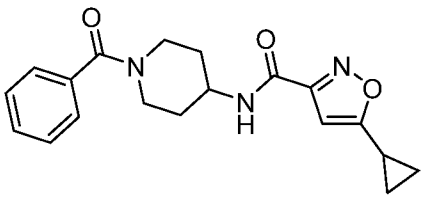
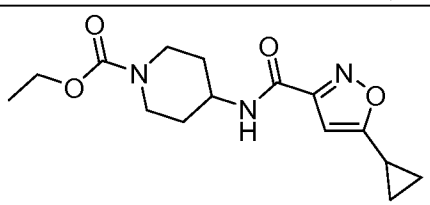
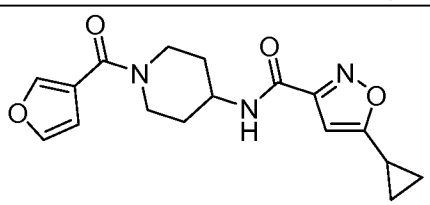
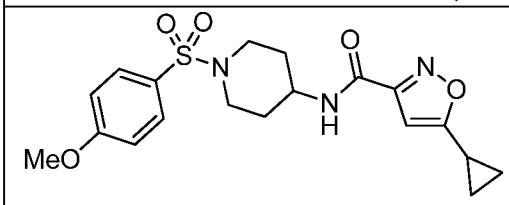
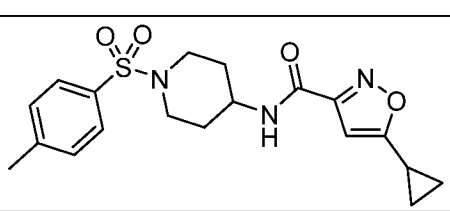
	5-cyclopropyl-N-(1-(methylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-isobutyrylpiperidin-4-yl)isoxazole-3-carboxamide
	N-(1-benzoylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	ethyl 4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate
	5-cyclopropyl-N-(1-(furan-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-((4-methoxyphenyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-tosylpiperidin-4-yl)isoxazole-3-carboxamide

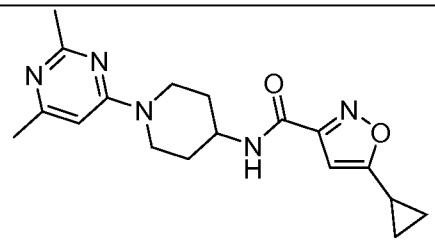
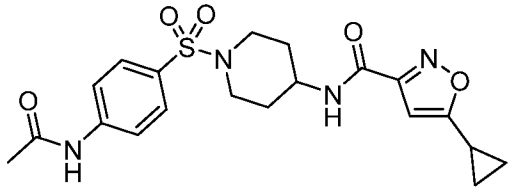
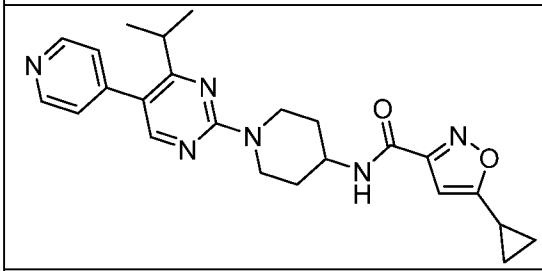
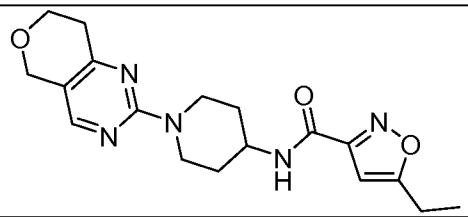
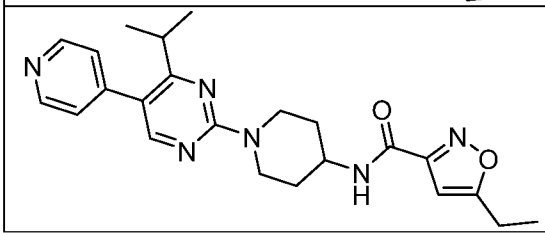
	5-cyclopropyl-N-(1-(2,6-dimethylpyrimidin-4-yl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-(7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)piperidin-4-yl)-5-ethylisoxazole-3-carboxamide
	5-ethyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide

and a pharmeceutically acceptable carier.

[0131] In some embodiments, the disclosure relates to a method of inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a subject, comprising administering to a subject in need thereof an effective amount of at least one of the following compounds:

Structure	Name
	5-cyclopropyl-N-(piperidin-4-yl)isoxazole-3-carboxamide
	N-(8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide

	N-(1-(2-amino-2-oxoethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(methylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-isobutyrylpiperidin-4-yl)isoxazole-3-carboxamide
	N-(1-benzoylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	ethyl 4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate
	5-cyclopropyl-N-(1-(furan-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-((4-methoxyphenyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide
	5-cyclopropyl-N-(1-tosylpiperidin-4-yl)isoxazole-3-carboxamide

	5-cyclopropyl-N-(1-(2,6-dimethylpyrimidin-4-yl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide
	5-cyclopropyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide
	N-(1-(7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)piperidin-4-yl)-5-ethylisoxazole-3-carboxamide
	5-ethyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide

Definitions

[0132] For the purpose of the present disclosure, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms (*i.e.*, C_{1-12} alkyl) or the number of carbon atoms designated (*i.e.,* a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, a C_3 alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is chosen from a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C_{3-10} alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C_{1-4} alkyl group. In another embodiment, the alkyl group is chosen

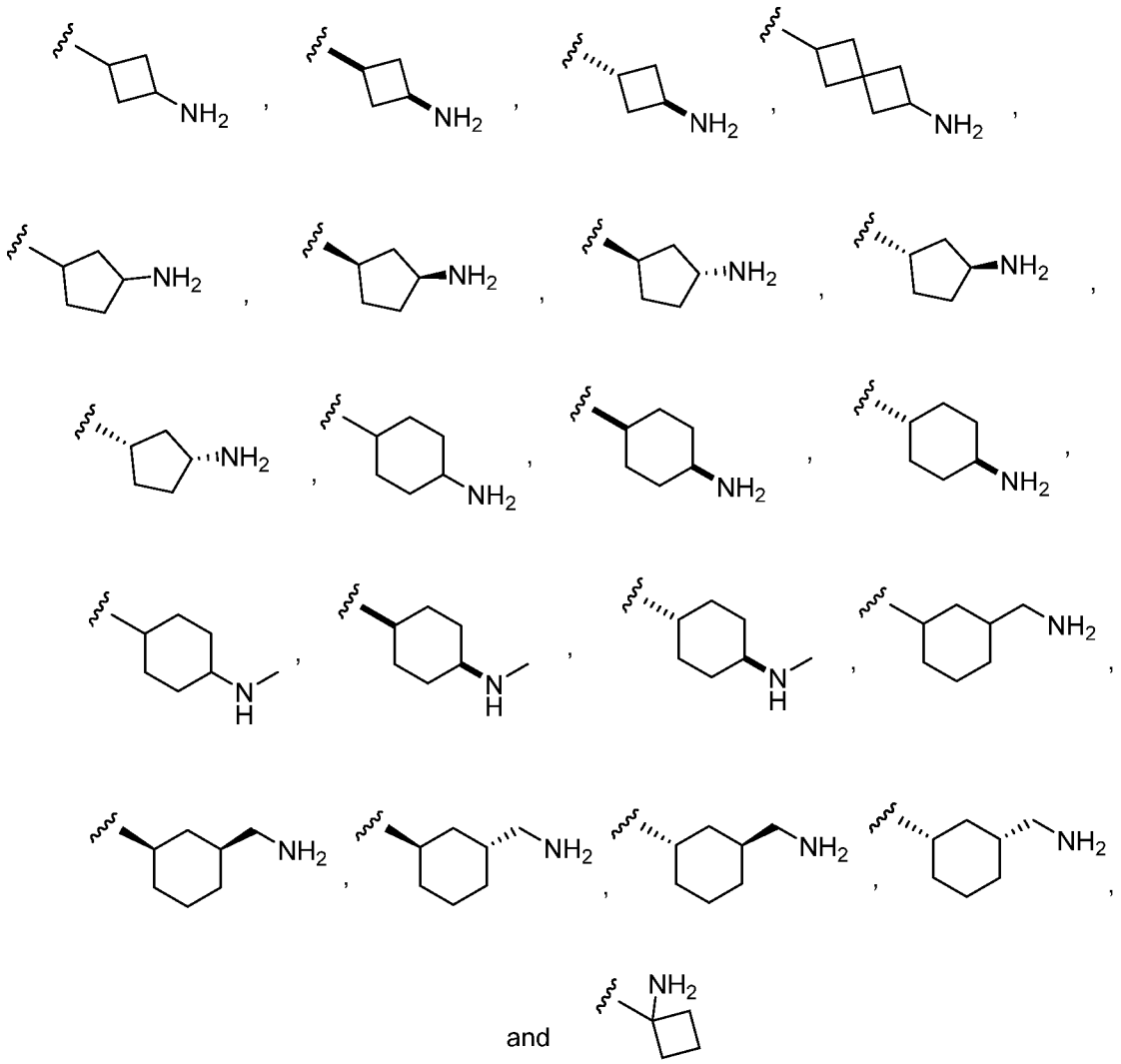
from a branched chain C_{3-4} alkyl group. In another embodiment, the alkyl group is chosen from a straight or branched chain C_{3-4} alkyl group. In another embodiment, the alkyl group is partially or completely deuterated, *i.e.*, one or more hydrogen atoms of the alkyl group are replaced with deuterium atoms. Non-limiting exemplary C_{1-10} alkyl groups include methyl (including $-CD_3$), ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. Non-limiting exemplary C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl. Non-limiting exemplary C_{1-4} groups include methyl, ethyl, propyl, isopropyl, and *tert*-butyl.

[0133] For the purpose of the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group means that the alkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, alkoxycarbonyl, and carboxyalkyl. In one embodiment, the alkyl is a C_{1-4} alkyl. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. Non-limiting exemplary optionally substituted alkyl groups include $-CH_2CH_2NO_2$, $-CH_2CH_2CO_2H$, $-CH_2CH_2SO_2CH_3$, $-CH_2CH_2COPh$, and $-CH_2C_6H_{11}$.

[0134] For the purpose of the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to saturated and partially unsaturated (containing one or two double bonds) cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms (*i.e.*, C_{3-12} cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl group has two rings. In one embodiment, the cycloalkyl group has one ring. In another embodiment, the cycloalkyl group is chosen from a C_{3-8} cycloalkyl group. In another embodiment, the cycloalkyl group is chosen from a C_{3-6} cycloalkyl group. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, and spiro[3.3]heptane.

[0135] For the purpose of the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group means that the cycloalkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino,

dialkylamino, aralkylamino, heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkylamino, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkyl is substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. In one embodiment, the optionally substituted cycloalkyl is substituted with at least one amino, alkylamino, or dialkylamino group. The term "amino-substituted cycloalkyl" as used by itself or as part of another group means that the optionally susbstituted cycloalkyl as defined above is substituted with at least one amino group. In one embodiment, the amino-substituted cycloalkyl is an amino-substituted cyclohexyl group. Non-limiting exemplary optionally substituted cycloalkyl groups include:



[0136] For the purpose of the present disclosure, the term "cycloalkenyl" as used by itself or part of another group refers to a partially unsaturated cycloalkyl group as defined above. In one embodiment, the cycloalkenyl has one carbon-to-carbon double bond. In another embodiment, the cycloalkenyl group is chosen from a C_{4-8} cycloalkenyl group. Exemplary cycloalkenyl groups include cyclopentenyl and cyclohexenyl.

[0137] For the purpose of the present disclosure, the term "optionally substituted cycloalkenyl" as used by itself or as part of another group means that the cycloalkenyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, heteroalkyl, haloalkyl, monohydroxyalkyl, dihydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally

substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkenyl is substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, monohydroxyalkyl, dihydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkenyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkenyl is substituted with one substituent. In another embodiment, the cycloalkenyl is unsubstituted.

[0138] For the purpose of the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is chosen from a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is chosen from a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0139] For the purpose of the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group means the alkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo.

[0140] For the purpose of the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one to three

carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In one embodiment, the alkynyl group is chosen from a C_{2-6} alkynyl group. In another embodiment, the alkynyl group is chosen from a C_{2-4} alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0141] For the purpose of the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part of another group means the alkynyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

[0142] For the purpose of the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl group substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is chosen from a C_{1-4} haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0143] For the purpose of the present disclosure, the term "fluoroalkyl" as used by itself or as part of another group refers to an alkyl group substituted by one or more fluorine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine atoms. In another embodiment, the fluoroalkyl group is chosen from a C_{1-4} fluoroalkyl group. Non-limiting exemplary fluoroalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and 4,4,4-trifluorobutyl.

[0144] For the purpose of the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more, *e.g.*, one, two, or three, hydroxy groups. In one embodiment, the hydroxyalkyl group is a monohydroxyalkyl group, *i.e.,* substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, *i.e.,* substituted with two

hydroxy groups. In another embodiment, the hydroxyalkyl group is chosen from a C_{1-4} hydroxyalkyl group. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[0145] For the purpose of the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is chosen from a C_{1-4} alkoxy group. In another embodiment, the alkoxy group is chosen from a C_{1-4} alkyl attached to a terminal oxygen atom, *e.g.,* methoxy, ethoxy, and *tert*-butoxy.

[0146] For the purpose of the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to a sulfur atom substituted by an optionally substituted alkyl group. In one embodiment, the alkylthio group is chosen from a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-SCH_3$, and $-SCH_2CH_3$.

[0147] For the purpose of the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkoxy group. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

[0148] For the purpose of the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

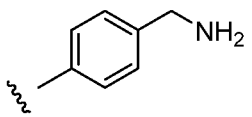
[0149] For the purpose of the present disclosure, the term "heteroalkyl" as used by itself or part of another group refers to a stable straight or branched chain hydrocarbon radical containing 1 to 10 carbon atoms and at least two heteroatoms, which can be the same or different, selected from O, N, or S, wherein: 1) the nitrogen atom(s) and sulfur atom(s) can optionally be oxidized; and/or 2) the nitrogen atom(s) can optionally be quaternized. The heteroatoms can be placed at any interior position of the heteroalkyl group or at a position at which the heteroalkyl group is attached to the remainder of the molecule.

In one embodiment, the heteroalkyl group contains two oxygen atoms. In one embodiment, the heteroalkyl contains one oxygen and one nitrogen atom. In one embodiment, the heteroalkyl contains two nitrogen atoms. Non-limiting exemplary heteroalkyl groups include $-CH_2OCH_2CH_2OCH_3$, $-OCH_2CH_2OCH_2CH_2OCH_3$, $-CH_2NHCH_2CH_2OCH_2$, $-OCH_2CH_2NH_2$, $-NHCH_2CH_2N(H)CH_3$, $-CH_2CH_2CH_2N(H)CH_2CH_2NH_2$, $-CH_2CH_2CH_2N(H)CH_2CH_2N(H)CH_3$, $-NHCH_2CH_2OCH_3$, $-N(CH_3)CH_2CH_2CH_2OCH_3$, and $-OCH_2CH_2OCH_3$.

[0150] For the purpose of the present disclosure, the term "aryl" as used by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring system having from six to fourteen carbon atoms (*i.e.*, C_{6-14} aryl). Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is chosen from phenyl or naphthyl. In one embodiment, the aryl group is phenyl.

[0151] For the purpose of the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group means that the aryl as defined above is either unsubstituted or substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (C_{1-4} haloalkoxy)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, and $-N(H)C(=O)-R^{45}$, wherein R^{43} is hydrogen or C_{1-4} alkyl; R^{44} is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl; and R^{45} is alkyl, optionally substituted aryl or optionally substituted heteroaryl. In one embodiment, the optionally substituted aryl is substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl,

optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (C_{1-4} haloalkoxy)alkyl, (heteroaryl)alkyl, -N(R^{43})(R^{44}), and -N(H)C(=O)-R^{45}. In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. In another embodiment, the optionally substituted phenyl has at least one amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl substituent. The term "(amino)alkyl-substituted phenyl" as used by itself or as part of another group means that the optionally susbstituted phenyl as defined above is substituted with at least one (amino)alkyl group. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, 2-phenylpropan-2-amine,



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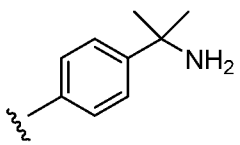
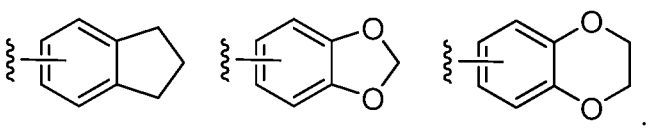


The term optionally substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include:



[0152] For the purpose of the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

[0153] For the purpose of the present disclosure, the term "heteroaryloxy" as used by itself or as part of another group refers to an optionally substituted heteroaryl attached to a terminal oxygen atom.

[0154] For the purpose of the present disclosure, the term "aralkyloxy" or "arylalkyloxy" as used by itself or as part of another group refers to an aralkyl group attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is $PhCH_2O$-.

[0155] For the purpose of the present disclosure, the term "heteroaryl" or "heteroaromatic" refers to monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms (*i.e.*, a 5- to 14-membered heteroaryl) and 1, 2, 3, or 4 heteroatoms independently chosen from oxygen, nitrogen or sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In another embodiment, the heteroaryl has 5 ring atoms, e.g., thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another embodiment, the heteroaryl has 6 ring atoms, e.g., pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (*e.g.*, thien-2-yl and thien-3-yl), furyl (*e.g.*, 2-furyl and 3-furyl), pyrrolyl (*e.g.*, 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (*e.g.*, 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (*e.g.*, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (*e.g.*, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (*e.g.*, pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (*e.g.*, thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl),

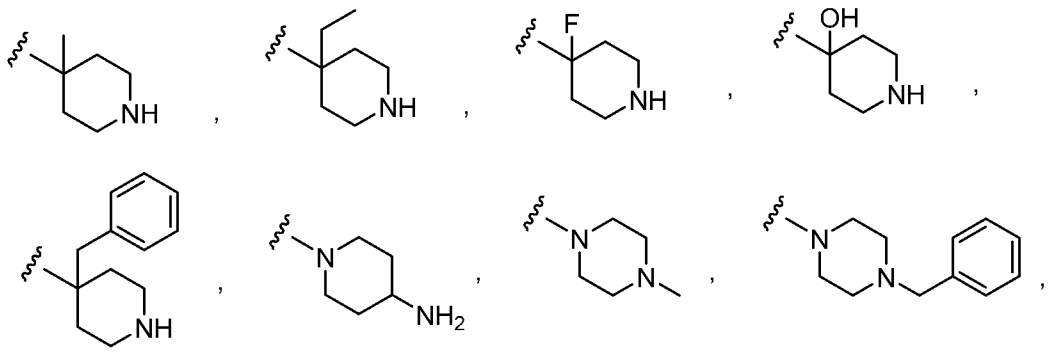
oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (*e.g.*, isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term "heteroaryl" is also meant to include possible N-oxides. Exemplary N-oxides include pyridyl N-oxide.

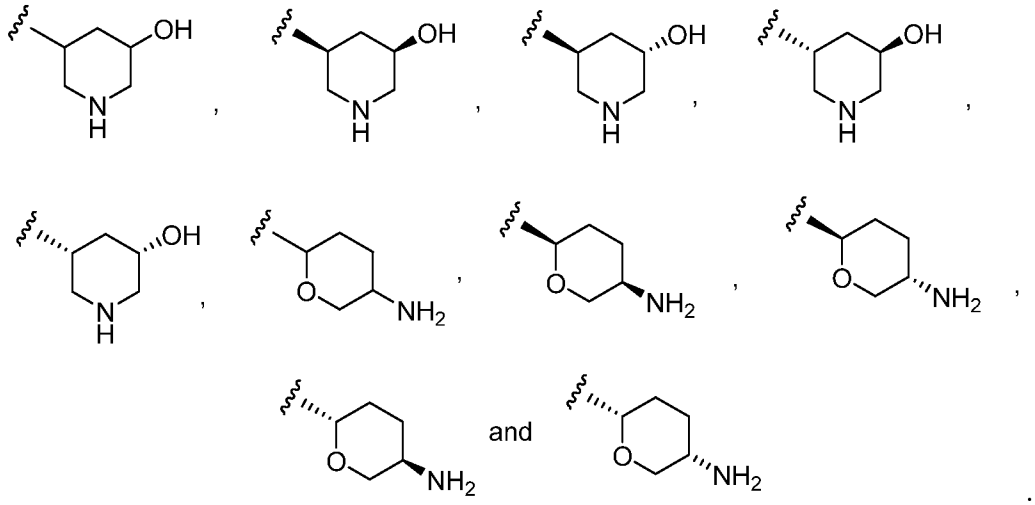
[0156] For the purpose of the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group means that the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, *e.g.*, one or two substituents, independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aralkyl, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$, wherein R^{43} is hydrogen or C_{1-4} alkyl; R^{44} is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl; and R^{45} is alkyl, optionally substituted aryl, or optionally substituted heteroaryl. In another embodiment, the optionally substituted heteroaryl is substituted with one to four substituents, *e.g.*, one or two substituents, independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aralkyl, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$. In one embodiment, the optionally substituted heteroaryl has one substituent. In one embodiment, the substituent is amino, alkylamino, dialkylamino, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$. In one embodiment, the optionally substituted is an optionally substituted pyridyl, *i.e.,* 2-, 3-, or 4-pyridyl. Any available carbon or nitrogen atom can be substituted.

[0157] For the purpose of the present disclosure, the term "heterocycle" or "heterocyclo" as used by itself or as part of another group refers to saturated and partially unsaturated (*e.g.,* containing one or two double bonds) cyclic groups containing one, two, or three rings having from three to fourteen ring members (*i.e.*, a 3- to 14-membered heterocyclo) and at least one heteroatom. Each heteroatom is independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be quaternized. The term "heterocyclo" is meant to include cyclic ureido groups such as imidazolidinyl-2-one, cyclic amide groups such as β-lactam, γ-lactam, δ-lactam and ε-lactam, and cyclic carbamate groups such as oxazolidinyl-2-one. The term "heterocyclo" is also meant to include groups having fused optionally substituted aryl groups, *e.g.*, indolinyl, indolinyl-2-one, benzo[d]oxazolyl-2(3H)-one. In one embodiment, the heterocyclo group is chosen from a 4-, 5-, 6-, 7- or 8-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 5- or 6-membered cyclic group containing one ring and one or two nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 8-, 9-, 10-, 11-, or 12-membered cyclic group containing two rings and one or two nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include 2-oxopyrrolidin-3-yl, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, 8-azabicyclo[3.2.1]octane (nortropane), 6-azaspiro[2.5]octane, 6-azaspiro[3.4]octane, indolinyl, indolinyl-2-one, 1,3-dihydro-2H-benzo[d]imidazol-2-one.

[0158] For the purpose of the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkylamino, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl,

(heterocyclo)alkyl, and (heteroaryl)alkyl. Substitution may occur on any available carbon or nitrogen atom, and may form a spirocycle. In another embodiment, the optionally substituted heterocyclo is substituted with one to four substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, aralkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted heterocyclo is substituted with at least one amino, alkylamino, or dialkylamino group. The term "amino-substituted heterocyclo" as used by itself or as part of another group means that the optionally susbstituted heterocyclo as defined above is substituted with at least one amino group. Likewise, the term "alkylamino-substituted heterocyclo" as used by itself or as part of another group means that the optionally susbstituted heterocyclo as defined above is substituted with at least one alkylamino group. In one embodiment, the amino-substituted or alkylamino-substituted heterocyclo is an amino-substituted or alkylamino-substituted piperidine. Non-limiting exemplary optionally substituted heterocyclo groups include:





[0159] For the purpose of the present disclosure, the term "amino" as used by itself or as part of another group refers to $-NH_2$.

[0160] For the purpose of the present disclosure, the term "alkylamino" as used by itself or as part of another group refers to $-NHR^{22}$, wherein R^{22} is C_{1-6} alkyl. In one embodiment, R^{22} is C_{1-4} alkyl. Non-limiting exemplary alkylamino groups include $-N(H)CH_3$ and $-N(H)CH_2CH_3$.

[0161] For the purpose of the present disclosure, the term "dialkylamino" as used by itself or as part of another group refers to $-NR^{23a}R^{23b}$, wherein R^{23a} and R^{23b} are each independently C_{1-6} alkyl. In one embodiment, R^{23a} and R^{23b} are each independently C_{1-4} alkyl. Non-limiting exemplary dialkylamino groups include $-N(CH_3)_2$ and $-N(CH_3)CH_2CH(CH_3)_2$.

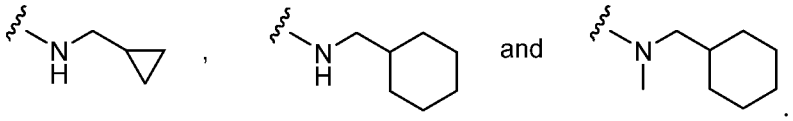
[0162] For the purpose of the present disclosure, the term "hydroxyalkylamino" as used by itself or as part of another group refers to $-NHR^{24}$, wherein R^{24} is hydroxyalkyl.

[0163] For the purpose of the present disclosure, the term "cycloalkylamino" as used by itself or as part of another group refers to $-NR^{25a}R^{25b}$, wherein R^{25a} is optionally substituted cycloalkyl and R^{25b} is hydrogen or C_{1-4} alkyl.

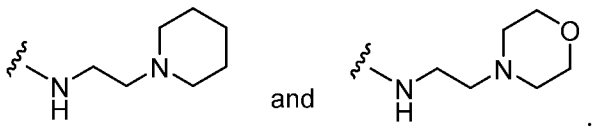
[0164] For the purpose of the present disclosure, the term "aralkylamino" as used by itself or as part of another group refers to $-NR^{26a}R^{26b}$, wherein R^{26a} is aralkyl and R^{26b} is hydrogen or C_{1-4} alkyl. Non-limiting exemplary aralkylamino groups include $-N(H)CH_2Ph$, $-N(H)CHPh_2$, and $-N(CH_3)CH_2Ph$.

[0165] For the purpose of the present disclosure, the term "(cycloalkyl)alkylamino" as used by itself or as part of another group refers to $-NR^{26c}R^{26d}$, wherein R^{26c} is

(cycloalkyl)alkyl and R^{26d} is hydrogen or C_{1-4} alkyl. Non-limiting exemplary (cycloalkyl)alkylamino groups include:



[0166] For the purpose of the present disclosure, the term "(heterocyclo)alkylamino" as used by itself or as part of another group refers to $-NR^{26e}R^{26f}$, wherein R^{26e} is (heterocyclo)alkyl and R^{26f} is hydrogen or C_{1-4} alkyl. Non-limiting exemplary (heterocyclo)alkylamino groups include:



[0167] For the purpose of the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an amino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (amino)alkyl groups include $-CH_2NH_2$, $-C(CH_3)NH_2$, $-C(NH_2)(H)CH_3$, $-CH_2CH_2NH_2$, $-CH_2C(NH_2)(H)CH_3$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, and $-CH_2C(CH_3)_2CH_2NH_2$.

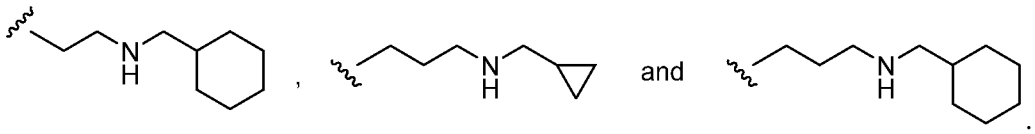
[0168] For the purpose of the present disclosure, the term "(alkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. A non-limiting exemplary (alkylamino)alkyl group is $-CH_2CH_2N(H)CH_3$.

[0169] For the purpose of the present disclosure, the term "(dialkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a dialkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (dialkylamino)alkyl groups are $-CH_2CH_2N(CH_3)_2$.

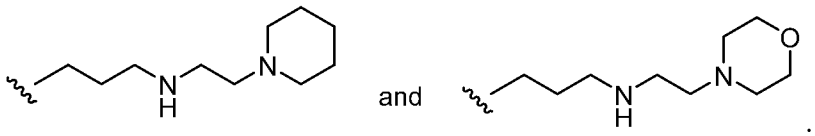
[0170] For the purpose of the present disclosure, the term "(cycloalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a cycloalkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (cycloalkylamino)alkyl groups include $-CH_2N(H)$cyclopropyl, $-CH_2N(H)$cyclobutyl, and $-CH_2N(H)$cyclohexyl.

[0171] For the purpose of the present disclosure, the term "[(cycloalkyl)alkylamino]alkyl" as used by itself or as part of another group refers to an

alkyl group substituted by a (cycloalkyl)alkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary ([(cycloalkyl)alkylamino]alkyl groups include:



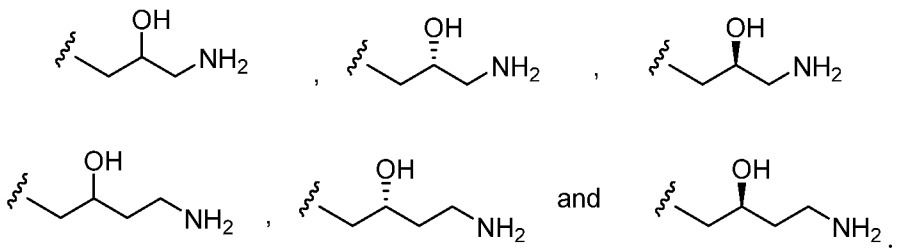
[0172] For the purpose of the present disclosure, the term "[(heterocyclo)alkylamino]alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a (heterocyclo)alkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary ([(heterocyclo)alkylamino]alkyl groups include:



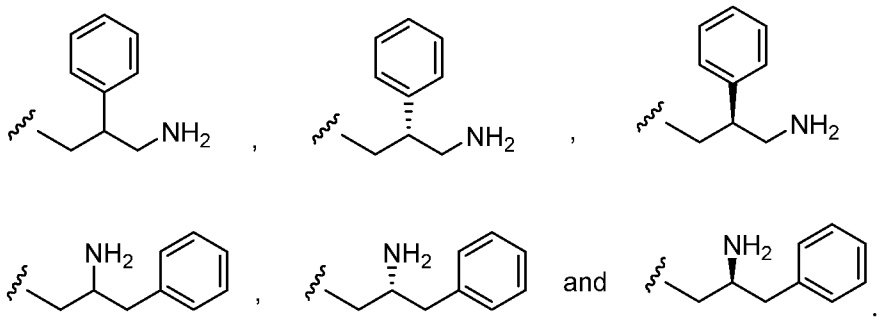
[0173] For the purpose of the present disclosure, the term "(aralkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an aralkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (aralkylamino)alkyl groups include $-CH_2CH_2CH_2N(H)CH_2Ph$ and $-CH_2CH_2CH_2N(H)CH_2(4\text{-}CF_3\text{-}Ph)$.

[0174] For the purpose of the present disclosure, the term "(cyano)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more cyano, *e.g.,* -CN, groups. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (cyano)alkyl groups include $-CH_2CH_2CN$, $-CH_2CH_2CH_2CN$, and $-CH_2CH_2CH_2CH_2CN$.

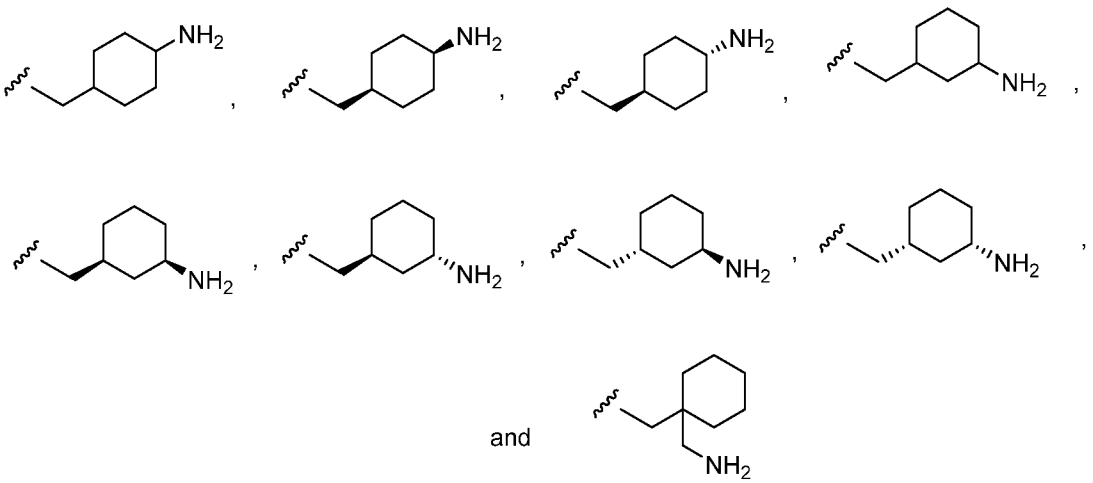
[0175] For the purpose of the present disclosure, the term "(amino)(hydroxy)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one hydroxy group. In one embodiment, the alkyl is a C_{1-6} alkyl. In another embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (amino)(hydroxy)alkyl groups include:



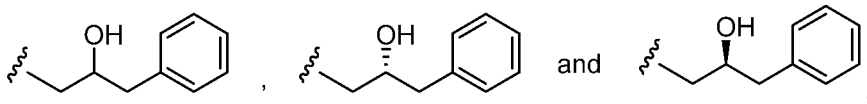
[0176] For the purpose of the present disclosure, the term "(amino)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one optionally substituted aryl group. In one embodiment, the alkyl is a C_{1-6} alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (amino)(aryl)alkyl groups include:



[0177] For the purpose of the present disclosure, the term "(cycloalkyl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one optionally substituted cycloalkyl group. In one embodiment, the alkyl is a C_{1-4} alkyl. In one embodiment, the cycloalkyl is a C_{3-6} cycloalkyl. In one embodiment, the optionally substituted cycloalkyl group is substituted with an amino or (amino)alkyl group. Non-limiting exemplary (cycloalkyl)alkyl groups include:



[0178] For the purpose of the present disclosure, the term "(hydroxy)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one hydroxy group and one optionally substituted aryl group. In one embodiment, the alkyl is a C_{1-6} alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (hydroxy)(aryl)alkyl groups include:



[0179] For the purpose of the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{26a}R^{26b}$, wherein R^{26a} and R^{26b} are each independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^{26a} and R^{26b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. In one embodiment, R^{26a} and R^{26b} are each independently hydrogen or optionally substituted alkyl. Non-limiting exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $CON(CH_3)_2$, and -CON(H)Ph.

[0180] For the purpose of the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with a carboxamido group. Non-limiting exemplary (carboxamido)alkyl groups include $-CH_2CONH_2$, $-C(H)CH_3-CONH_2$, and $-CH_2CON(H)CH_3$.

[0181] For the purpose of the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $-SO_2NR^{27a}R^{27b}$, wherein R^{27a} and R^{27b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{27a} and R^{27b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, and $-SO_2N(H)Ph$.

[0182] For the purpose of the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by an alkyl group. A non-limiting exemplary alkylcarbonyl group is $-COCH_3$.

[0183] For the purpose of the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is -COPh.

[0184] For the purpose of the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-SO_2-$, substituted by any of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-SO_2CH_3$.

[0185] For the purpose of the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-SO_2-$, substituted by any of

the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is -SO_2Ph.

[0186] For the purpose of the present disclosure, the term "mercaptoalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted by a –SH group.

[0187] For the purpose of the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula -COOH.

[0188] For the purpose of the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a -COOH. A non-limiting exemplary carboxyalkyl group is -CH_2CO_2H.

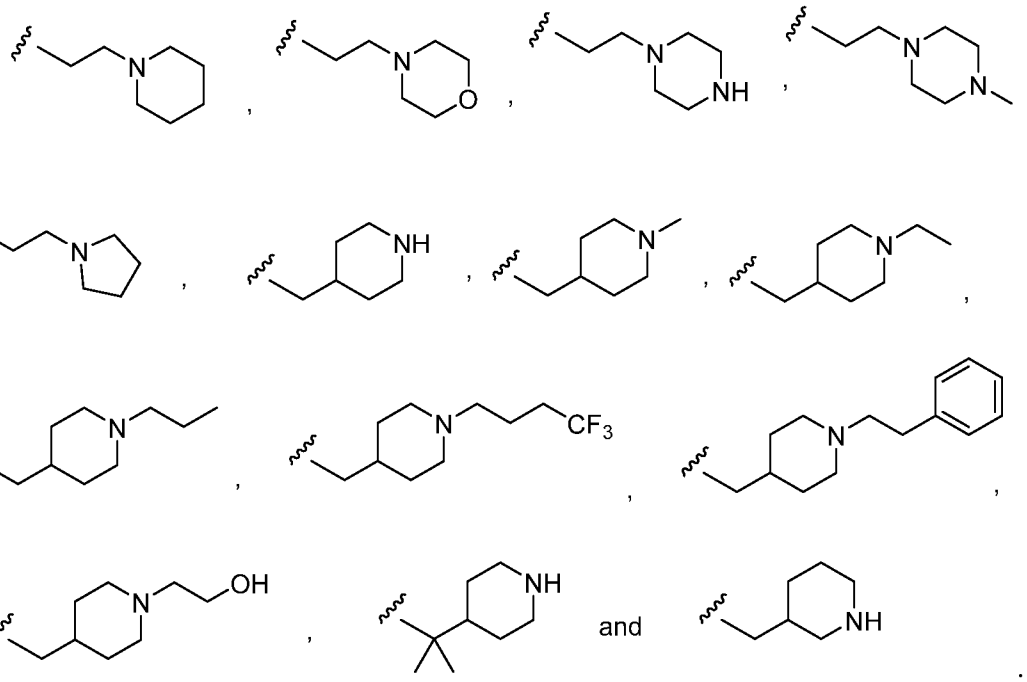
[0189] For the purpose of the present disclosure, the term "alkoxycarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by an alkoxy group. In one embodiment, the alkoxy group is a C_{1-4} alkoxy. Non-limiting exemplary alkoxycarbonyl groups are -CO_2Me and -CO_2Et.

[0190] For the purpose of the present disclosure, the term "aralkyl" or "arylalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the aralkyl group is a C_{1-4} alkyl substituted with one optionally substituted aryl group. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, -$CHPh_2$, -CH_2(4-OH-Ph), and -CH(4-F-Ph)$_2$.

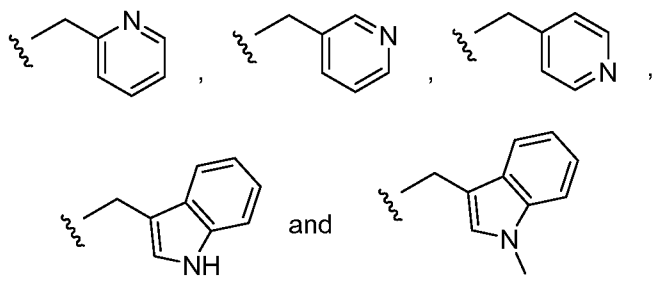
[0191] For the purpose of the present disclosure, the term "ureido" as used by itself or as part of another group refers to a radical of the formula -NR^{30a}-C(=O)-$NR^{30b}R^{30c}$, wherein R^{30a} is hydrogen, alkyl, or optionally substituted aryl, and R^{30b} and R^{30c} are each independently hydrogen, alkyl, or optionally substituted aryl, or R^{30b} and R^{30c} taken together with the nitrogen to which they are attached form a 4- to 8-membered heterocyclo group. Non-limiting exemplary ureido groups include -NH-C(C=O)-NH_2 and -NH-C(C=O)-$NHCH_3$.

[0192] For the purpose of the present disclosure, the term "guanidino" as used by itself or as part of another group refers to a radical of the formula -NR^{28a}-C(=NR^{29})-$NR^{28b}R^{28c}$, wherein R^{28a}, R^{28b}, and R^{28c} are each independently hydrogen, alkyl, or optionally substituted aryl, and R^{29} is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include -NH-C(C=NH)-NH_2, -NH-C(C=NCN)-NH_2, and -NH-C(C=NH)-$NHCH_3$.

[0193] For the purpose of the present disclosure, the term "(heterocyclo)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heterocyclo groups. In one embodiment, the (heterocyclo)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heterocyclo group. The heterocyclo can be linked to the alkyl group through a carbon or nitrogen atom. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0194] For the purpose of the present disclosure, the term "(heteroaryl)alkyl" or "heteroaralkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl group is a C_{1-4} alkyl substituted with one optionally substituted heteroaryl group. Non-limiting exemplary (heteroaryl)alkyl groups include:



[0195] For the purpose of the present disclosure, the term "alkylcarbonylamino" as used by itself or as part of another group refers to an alkylcarbonyl group attached to an amino. A non-limiting exemplary alkylcarbonylamino group is $-NHCOCH_3$.

[0196] For the purpose of the present disclosure, the term "C_{1-4} bridge" refers to a -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, or -$(CH_2)_4$- group that joins two carbon atoms of a piperidine to form an azabicyclo group. For example, in Formula **I**, R^{3a} and R^{4a} of B can be taken together to form a 6-azabicyclo[3.1.1]heptane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, or 10-azabicyclo[4.3.1]decane group. Each methylene unit of the C_{1-4} bridge can be optionally substituted with one or two substituents independently selected from the group consisting of C_{1-4} alkyl and halo.

[0197] The present disclosure encompasses any of the Compounds of the Disclosure being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H (or deuterium (D)), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively, *e.g.*, ^{3}H, ^{11}C, and ^{14}C. In one embodiment, provided is a composition wherein substantially all of the atoms at a position within the Compound of the Disclosure are replaced by an atom having a different atomic mass or mass number. In another embodiment, provided is a composition wherein a portion of the atoms at a position within the Compound of the disclosure are replaced, *i.e.*, the Compound of the Disclosure is enriched at a position with an atom having a different atomic mass or mass number." Isotopically-labelled Compounds of the Disclosure can be prepared by methods known in the art.

[0198] Compounds of the Disclosure may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure is meant to encompass the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present disclosure as well.

[0199] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0200] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0201] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[0202] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. In one embodiment, Compounds of the Disclosure are racemic.

[0203] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, *e.g.,* R or S.

[0204] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem 68*:2193 (1996), unless otherwise indicated.

[0205] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S|*100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{obs}/[\alpha]_{max})*100$, where $[\alpha]_{obs}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{max}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.

[0206] The terms "enantiomerically pure" or "enantiopure" refer to a sample of a chiral substance all of whose molecules (within the limits of detection) have the same chirality sense. In one embodiment, Compounds of the Disclosure are enantiomerically pure.

[0207] The terms "enantiomerically enriched" or "enantioenriched" refer to a sample of a chiral substance whose enantiomeric ratio is greater than 50:50. In one embodiment, Compounds of the Disclosure are enantiomerically enriched, *e.g.*, the enantiomeric ratio is about 60:40 or greater, about 70:30 or greater, about 80:20 or greater, about 90:10 or greater, about 95:5 or greater, about 98:2 or greater, or about 99:1 or greater. Enantiomerically enriched compounds may be enantiomerically pure.

[0208] The terms "a" and "an" refer to one or more.

[0209] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

[0210] The present disclosure encompasses the preparation and use of salts of the Compounds of the Disclosure, including non-toxic pharmaceutically acceptable salts. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparginate, glutamate and the like. The term "pharmaceutically acceptable salt" as used herein, refers to any salt, *e.g.*, obtained by reaction with an acid or a base, of a Compound of the Disclosure that is physiologically tolerated in the target patient (*e.g.*, a mammal, *e.g.,* a human).

[0211] Acid addition salts can be formed by mixing a solution of the particular Compound of the Disclosure with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the compound of the present disclosure with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

[0212] The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, *e.g.* a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about

1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0213] Since Compounds of the Disclosure are inhibitors of SMYD proteins, such as SMYD3 and SMYD2, a number of diseases, conditions, or disorders mediated by SMYD proteins, such as SMYD3 and SMYD2, can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a disease, condition, or disorder responsive to the inhibition of SMYD proteins, such as SMYD3 and SMYD2, in an animal suffering from, or at risk of suffering from, the disorder, the method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

[0214] The present disclosure is further directed to a method of inhibiting SMYD proteins in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0215] The present disclosure is further directed to a method of inhibiting SMYD3 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0216] The present disclosure is further directed to a method of inhibiting SMYD2 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0217] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need of such treatment.

[0218] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0219] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (*i.e.*, retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (*i.e.*, retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; modulate protein methylation in the target cells; and/or relieve, to some

extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[0220] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0221] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0222] The term "disease" or "condition" or "disorder" denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. As demonstrated below, Compounds of the Disclosure inhibit SMYD proteins, such as SMYD3 and SMYD2 and can be used in treating diseases and conditions such as proliferative diseases, wherein inhibition of SMYD proteins, such as SMYD3 and SMYD2 provides a benefit.

[0223] In some embodiments, the Compounds of the Disclosure can be used to treat a "SMYD protein mediated disorder" (*e.g.*, a SMYD3-mediated disorder or a SMYD2-mediated disorder). A SMYD protein mediated disorder is any pathological condition in which a SMYD protein is know to play a role. In some embodiments, a SMYD-mediated disorder is a proliferative disease.

[0224] In some embodiments inhibiting SMYD proteins, such as SMYD3 and SMYD2, is the inhibition of the activity of one or more activities of SMYD proteins such as SMYD3 and SMYD2. In some embodiments, the activity of the SMYD proteins such as SMYD3 and SMYD2 is the ability of the SMYD protein such as SMYD3 or SMYD2 to transfer a methyl group to a target protein (*e.g.,* histone). It should be appreciated that the activity of the one or more SMYD proteins such as SMYD3 and SMYD2 may be inhibited *in vitro* or *in vivo*. Examplary levels of inhibition of the activity one or more SMYD proteins such as SMYD3 and SMYD2 include at least 10% inhibition, at least 20% inhibition, at least 30% inhibition, at least 40% inhibition, at least 50% inhibition, at least 60% inhibition, at least 70% inhibition, at least 80% inhibition, at least 90% inhibition, and up to 100% inhibition.

[0225] The SMYD (SET and MYND domain) family of lysine methyltransferases (KMTs) plays pivotal roles in various cellular processes, including gene expression regulation and DNA damage response. The family of human SMYD proteins consists of SMYD1, SMYD2, SMYD3, SMYD4 and SMYD5. SMYD1, SMYD2, and SMYD3 share a high degree of sequence homology and, with the exception of SMYD5, human SMYD proteins harbor at least one C-terminal tetratrico peptide repeat (TPR) domain. (See *e.g.,* Abu-Farha et al. *J Mol Cell Biol* (2011) 3 (5) 301-308). The SMYD proteins have been found to be linked to various cancers (See *e.g.*, Hamamoto et al. *Nat Cell. Biol.* 2004, 6: 731-740), Hu et al. Canncer Research 2009, 4067-4072, and Komatsu et al. *Carcinogenesis* 2009, 301139-1146.)

[0226] SMYD3 is a protein methyltransferase found to be expressed at high levels in a number of different cancers (Hamamoto, R., *et al., Nat. Cell Biol.*, 6(8):731-40 (2004)). SMYD3 likely plays a role in the regulation of gene transcription and signal transduction pathways critical for survival of breast, liver, prostate and lung cancer cell lines (Hamamoto, R., *et al., Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al., Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al., Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al., J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al., Nature*, 510(7504):283-7 (2014)).

[0227] Genetic knockdown of SMYD3 leads to a decrease in proliferation of a variety of cancer cell lines (Hamamoto, R., *et al., Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al., Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al., Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al., J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al., Nature*, 510(7504):283-7 (2014)). Several studies employing RNAi-based technologies have shown that ablation of SMYD3 in hepatocellular carcinoma cell lines greatly reduces cell viability and that its pro-survival role is dependent on its catalytic activity (Hamamoto, R., *et al., Nat. Cell Biol.*, 6(8):731-40 (2004); Van Aller, G.S., *et al., Epigenetics*, 7(4):340-3 (2012)). Moreover, SMYD3 has also been shown to be a critical mediator of transformation resulting from gain of function mutations in the oncogene, KRAS for both pancreatic and lung adenocarcinoma in mouse models. The dependence of KRAS on SMYD3 was also shown to be dependent on its catalytic activity (Mazur, P.K., *et al., Nature*, 510(7504):283-7 (2014)). SMYD3 function has also been implicated in colerectal cancers and RNAi mediated knockdown of SMYD3 has been shown to

impair colerectal cell proliferation. (Peserico et al., *Cell Physiol.* 2015 Feb 28. doi: 10.1002/jcp.24975. [Epub ahead of print]).

[0228] Furthermore, SMYD3 function has also been shown to play a role in immunology and development. For instance, de Almeida reported that SMYD3 plays a role in generation of inducible regulatory T cells (iTreg) cells. In a mouse model of respiratory syncytial virus (RSV) infection, a model in which iTreg cells have a critical role in regulating lung pathogenesis, SMYD3-/- mice demonstrated exacerbation of RSV-induced disease related to enhanced proinflammatory responses and worsened pathogenesis within the lung (de Almeida et al. *Mucosal Immunol.* 2015 Feb 11. doi: 10.1038/mi.2015.4. [Epub ahead of print]). In addition, as to development, Proserpio et al. have shown the importance of SMYD3 in the regulation of skeletal muscle atrophy (Proserpio et al. Genes Dev. 2013 Jun 1;27(11):1299-312), while Fujii et al. have elucidated the role of SMYD3 in cardiac and skeletal muscle development (Fujii et al. *PLoS One*. 2011;6(8):e23491).

[0229] SMYD2 (SET and MYND domain-containing protein 2) was first characterized as protein that is a member of a sub-family of SET domain containing proteins which catalyze the site-specific transfer of methyl groups onto substrate proteins. SMYD2 was initially shown to have methyltransferase activity towards lysine 36 on histone H3 (H3K36) but has subsequently been shown to have both histone and non-histone methyltrasferase activity.

[0230] SMYD2 has been implicated in the pathogenesis of multiple cancers. It has been shown to be over-expressed, compared to matched normal samples, in tumors of the breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus and prostate, as well as hematologic malignancies such as AML, B- and T-ALL, CLL and MCL, suggesting a role for SMYD2 in the biology of these cancers. More specifically, studies using genetic knock-down of SMYD2 have demonstrated anti-proliferative effects in esophageal squamous cell carcinoma (ESCC), bladder carcinoma and cervical carcinoma cell lines. (See *e.g.,* Komatsu et al., *Carcinogenesis* 2009, 30, 1139, and Cho et al., *Neoplasia.* 2012 Jun;14(6):476-86). Moreover, high expression of SMYD2 has been shown to be a poor prognostic factor in both ESCC and pediatric ALL. (See e.g., Komatsu et al. *Br J Cancer.* 2015 Jan 20;112(2):357-64, and Sakamoto et al., *Leuk Res.* 2014 Apr;38(4):496-502). Recently, Nguyen et al., have shown that a small molecule inhibitor of SMYD2 (LLY-507) inhibited the proliferation of several esophageal, liver

and breast cancer cell lines in a dose-dependent manner. (Nguyen et al. *J Biol Chem.* 2015 Mar 30. pii: jbc.M114.626861. [Epub ahead of print]).

[0231] SMYD2 has also been implicated in immunology. For instance, Xu et al. have shown that SMYD2 is a negative regulator of macrophage activation by suppressing Interleukin-6 and TNF-alpha production. (Xu et al., J Biol Chem. 2015 Feb 27;290(9):5414-23).

[0232] In one aspect, the present disclosure provides a method of treating cancer in a patient comprising administering a therapeutically effective amount of a Compound of the Disclosure. While not being limited to a specific mechanism, in some embodiemtns, Compounds of the Disclorure can treat cancer by inhibiting SMYD proteins, such as SMYD3 and SMYD2. Examples of treatable cancers include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma

multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway

glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0233] In another embodiment, the cancer is breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus, or prostate cancer.

[0234] In another embodiment, the cancer is a hematologic malignancy such as acute myeloid leukemia (AML), B- and T-acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or mantle cell lymphoma (MCL).

[0235] In another embodiment, the cancer is esophageal squamous cell carcinoma (ESCC), bladder carcinoma, or cervical carcinoma.

[0236] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer.

[0237] In another embodiment, the present disclosure provides a therapeutic method of modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in the cancers mentioned above by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.

[0238] Compounds of the Disclosure can be administered to a mammal in the form of a raw chemical without any other components present. Compounds of the Disclosure can also be administered to a mammal as part of a pharmaceutical composition containing the compound combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients and auxiliaries. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and

nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0239] Pharmaceutical compositions within the scope of the present disclosure include all compositions where a Compound of the Disclosure is combined with one or more pharmaceutically acceptable carriers. In one embodiment, the Compound of the Disclosure is present in the composition in an amount that is effective to achieve its intended therapeutic purpose. While individual needs may vary, a determination of optimal ranges of effective amounts of each compound is within the skill of the art. Typically, a Compound of the Disclosure can be administered to a mammal, *e.g.*, a human, orally at a dose of from about 0.0025 to about 1500 mg per kg body weight of the mammal, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof, per day to treat the particular disorder. A useful oral dose of a Compound of the Disclosure administered to a mammal is from about 0.0025 to about 50 mg per kg body weight of the mammal, or an equivalent amount of the pharmaceutically acceptable salt or solvate thereof. For intramuscular injection, the dose is typically about one-half of the oral dose.

[0240] A unit oral dose may comprise from about 0.01 mg to about 1 g of the Compound of the Disclosure, *e.g.,* about 0.01 mg to about 500 mg, about 0.01 mg to about 250 mg, about 0.01 mg to about 100 mg, 0.01 mg to about 50 mg, *e.g.*, about 0.1 mg to about 10 mg, of the compound. The unit dose can be administered one or more times daily, *e.g.*, as one or more tablets or capsules, each containing from about 0.01 mg to about 1 g of the compound, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof.

[0241] A pharmaceutical composition of the present disclosure can be administered to any patient that may experience the beneficial effects of a Compound of the Disclosure. Foremost among such patients are mammals, *e.g.*, humans and companion animals, although the disclosure is not intended to be so limited. In one embodiment, the patient is a human.

[0242] A pharmaceutical composition of the present disclosure can be administered by any means that achieves its intended purpose. For example, administration can be by the oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intranasal, transmucosal, rectal, intravaginal or buccal route, or by inhalation. The

dosage administered and route of administration will vary, depending upon the circumstances of the particular subject, and taking into account such factors as age, gender, health, and weight of the recipient, condition or disorder to be treated, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0243] In one embodiment, a pharmaceutical composition of the present disclosure can be administered orally. In another embodiment, a pharmaceutical composition of the present disclosure can be administered orally and is formulated into tablets, dragees, capsules, or an oral liquid preparation. In one embodiment, the oral formulation comprises extruded multiparticulates comprising the Compound of the Disclosure.

[0244] Alternatively, a pharmaceutical composition of the present disclosure can be administered rectally, and is formulated in suppositories.

[0245] Alternatively, a pharmaceutical composition of the present disclosure can be administered by injection.

[0246] Alternatively, a pharmaceutical composition of the present disclosure can be administered transdermally.

[0247] Alternatively, a pharmaceutical composition of the present disclosure can be administered by inhalation or by intranasal or transmucosal administration.

[0248] Alternatively, a pharmaceutical composition of the present disclosure can be administered by the intravaginal route.

[0249] A pharmaceutical composition of the present disclosure can contain from about 0.01 to 99 percent by weight, *e.g.*, from about 0.25 to 75 percent by weight, of a Compound of the Disclosure, *e.g.*, about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, or about 75% by weight of a Compound of the Disclosure.

[0250] A pharmaceutical composition of the present disclosure is manufactured in a manner which itself will be known in view of the instant disclosure, for example, by means of conventional mixing, granulating, dragee-making, dissolving, extrusion, or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active compound with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0251] Suitable excipients include fillers such as saccharides (for example, lactose, sucrose, mannitol or sorbitol), cellulose preparations, calcium phosphates (for example, tricalcium phosphate or calcium hydrogen phosphate), as well as binders such as starch paste (using, for example, maize starch, wheat starch, rice starch, or potato starch), gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, one or more disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate.

[0252] Auxiliaries are typically flow-regulating agents and lubricants such as, for example, silica, talc, stearic acid or salts thereof (*e.g.*, magnesium stearate or calcium stearate), and polyethylene glycol. Dragee cores are provided with suitable coatings that are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate can be used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0253] Examples of other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, or soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain a compound in the form of granules, which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers, or in the form of extruded multiparticulates. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

[0254] Possible pharmaceutical preparations for rectal administration include, for example, suppositories, which consist of a combination of one or more active compounds with a suppository base. Suitable suppository bases include natural and synthetic triglycerides, and paraffin hydrocarbons, among others. It is also possible to use gelatin

rectal capsules consisting of a combination of active compound with a base material such as, for example, a liquid triglyceride, polyethylene glycol, or paraffin hydrocarbon.

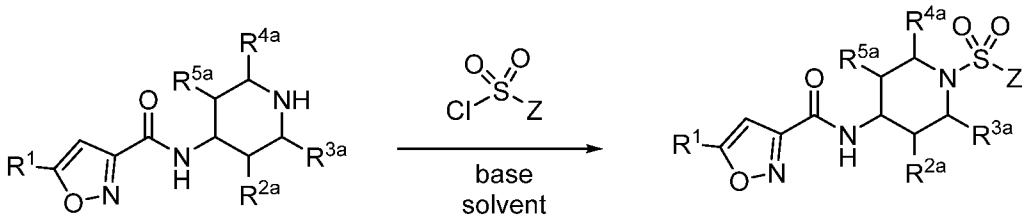
[0255] Suitable formulations for parenteral administration include aqueous solutions of the active compound in a water-soluble form such as, for example, a water-soluble salt, alkaline solution, or acidic solution. Alternatively, a suspension of the active compound can be prepared as an oily suspension. Suitable lipophilic solvents or vehicles for such as suspension may include fatty oils (for example, sesame oil), synthetic fatty acid esters (for example, ethyl oleate), triglycerides, or a polyethylene glycol such as polyethylene glycol-400 (PEG-400). An aqueous suspension may contain one or more substances to increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. The suspension may optionally contain stabilizers.

[0256] In another embodiment, the present disclosure provides kits which comprise a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

General Synthesis of Compounds

[0257] Compounds of the Disclosure are prepared using methods known to those skilled in the art in view of this disclosure, or by the illustrative methods shown in the General Schemes below. In the General Schemes, R^1, R^{2a}, R^{3b}, R^{3b}, R^{4a}, R^{5a}, and Z of Formulae **A-D** are as defined in connection with Formula **I**, unless otherwise indicated. In any of the General Schemes, suitable protecting can be employed in the synthesis, for example, when Z is (amino)alkyl or any other group that may group that may require protection, or when R^8 is amino, (amino)alkyl, or any other group that may requie protection. (See, Wuts, P. G. M.; Greene, T. W., "Greene's Protective Groups in Organic Synthesis", 4th Ed., J. Wiley & Sons, NY, 2007).

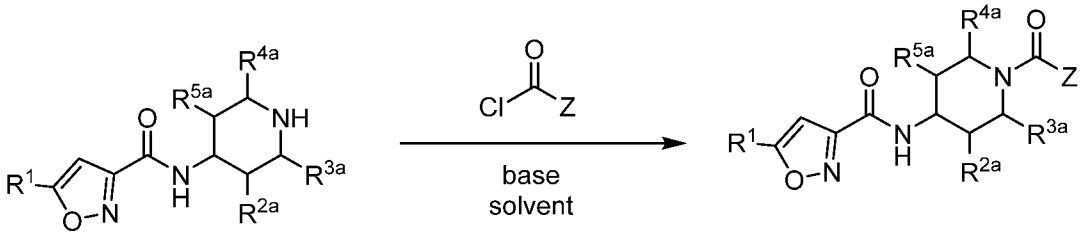
General Scheme 1



A B

[0258] Compound A is converted to compound B (i.e, a compound having Formula **I**, wherein R^{2b}, R^{3b}, R^{4b}, R^{5b}, and R^{6} are each hydrogen, and X is $-S(=O)_2-$) by coupling with a suitable sulfonyl chloride ($Z-SO_2Cl$) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

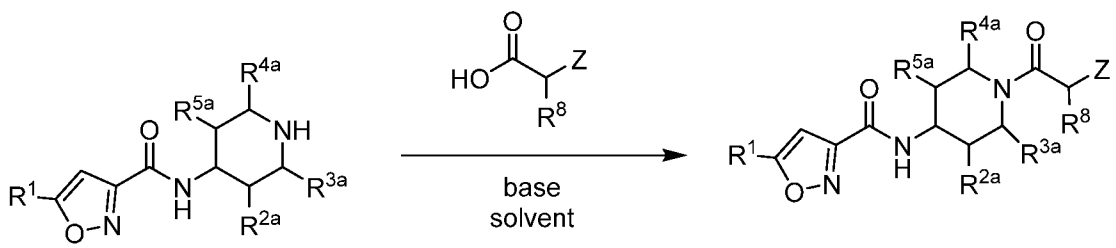
General Scheme 2



A C

[0259] Compound A is converted to compound C (i.e, a compound having Formula **I**, wherein R^{2b}, R^{3b}, R^{4b}, R^{5b}, and R^{6} are each hydrogen, and X is -C(=O)-) by coupling with a suitable acide chloride (Z-COCl) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF, or by coupling with a suitable carboxylic acid ($Z-CO_2H$) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

General Scheme 3



A D

[0260] Compound A is converted to compound D (i.e, a compound having Formula **I**, wherein R^{2b}, R^{3b}, R^{4b}, R^{5b}, and R^{6} are each hydrogen, and X is $-C(=O)C(R^{8})(H)-$) by

coupling with a suitable carboxylic acid (Z-C(H)R^8-CO_2H) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

EXAMPLES

General Synthetic Methods

[0261] General methods and experimental procedures for preparing and characterizing compounds of Tables 1-3 are set forth in the general schemes above and the examples below. Wherever needed, reactions were heated using conventional hotplate apparatus or heating mantle or microwave irradiation equipment. Reactions were conducted with or without stirring, under atmospheric or elevated pressure in either open or closed vessels. Reaction progress was monitored using conventional techniques such as TLC, HPLC, UPLC, or LCMS using instrumentation and methods described below. Reactions were quenched and crude compounds isolated using conventional methods as described in the specific examples provided. Solvent removal was carried out with or without heating, under atmospheric or reduced pressure, using either a rotary or centrifugal evaporator.

[0262] Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates. Compound purity and mass confirmations were conducted using standard HPLC and / or UPLC and / or MS spectrometers and / or LCMS and / or GC equipment (*i.e.,* including, but not limited to the following instrumentation: Waters Alliance 2695 with 2996 PDA detector connected with ZQ detector and ESI source; Shimadzu LDMS-2020; Waters Acquity H Class with PDA detector connected with SQ detector and ESI source; Agilent 1100 Series with PDA detector; Waters Alliance 2695 with 2998 PDA detector; AB SCIEX API 2000 with ESI source; Agilent 7890 GC). Exemplified compounds were dissolved in either MeOH or MeCN to a concentration of approximately 1 mg/mL and analyzed by injection of 0.5-10 μL into an appropriate LCMS system using the methods provided in the following table. In each case the flow rate is 1 mL/min. LCMS data are presented in Tables 1A, 2A, and 3A.

Method	Column	Mobile Phase A	Mobile Phase B	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
A	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/ 0.05% TFA	ACN/ 0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.2 minutes, then stop	250	1.5
B	Gemini-NX 3µm C18 110A	Water / 0.04% Ammonia	ACN	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	200	0.75
C	Shim-pack XR-ODS 1.6µm 2.0x50mm	Water/ 0.05% TFA	ACN/ 0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.85
D	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/ 0.05% TFA	ACN/ 0.05% TFA	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95

[0263] Compound structure confirmations were carried out using standard 300 or 400 MHz NMR spectrometers with nOe's conducted whenever necessary.

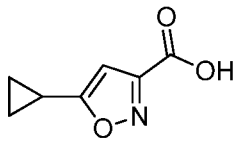
[0264] The following abbreviations are used herein:

Abbreviation	Meaning
ACN	acetonitrile
atm.	atmosphere
DCM	dichloromethane
DHP	dihydropyran
DIBAL	diisobutyl aluminum hydride
DIEA	diisopropyl ethylamine
DMF	dimethyl formamide
DMF-DMA	dimethyl formamide dimethyl acetal
DMSO	dimethyl sulfoxide
Dppf	1,1′-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
ESI	electrospray ionization
EtOH	Ethanol
FA	formic acid
GC	gas chromatography
H	hour
Hex	hexanes
HMDS	hexamethyl disilazide
HPLC	high performance liquid chromatography
IPA	Isopropanol
LCMS	liquid chromatography / mass spectrometry
MeOH	Methanol
Min	Minutes
NBS	*N*-bromo succinimide
NCS	*N*-chloro succinimide
NIS	*N*-iodo succinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Prep.	Preparative
PTSA	*para*-toluene sulfonic acid
Rf	retardation factor
rt	room temperature
RT	retention time
sat.	Saturated
SGC	silica gel chromatography
TBAF	tetrabutyl ammonium fluoride
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran

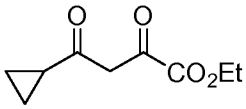
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography

EXAMPLE 1

Synthesis of 5-cyclopropylisoxazole-3-carboxylic acid

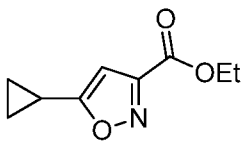


Step 1: Synthesis of ethyl 4-cyclopropyl-2,4-dioxobutanoate



[0265] Into a 10-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen Na (164 g, 1.20 equiv) was added in portions to ethanol (5 L). A solution of $(CO_2Et)_2$ (869 g, 1.00 equiv) and 1-cyclopropylethan-1-one (500 g, 5.94 mol, 1.00 equiv) was added dropwise with stirring at 0-20°C. The resulting solution was stirred for 1 h at 20-30° C and then for an additional 1 h at 80°C. The resulting solution was diluted with 15 L of H_2O. The pH was adjusted to 2 with hydrochloric acid (12N). The resulting solution was extracted with ethyl acetate and the organic layers combined and washed with $NaHCO_3$ (sat. aq.). The extract was concentrated under vacuum yielding 820 g (crude) of ethyl 4-cyclopropyl-2,4-dioxobutanoate as yellow oil. TLC (ethyl acetate/petroleum ether =1/5): Rf = 0.5.

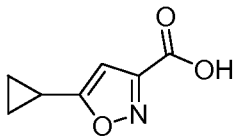
Step 2: Synthesis of ethyl 5-cyclopropylisoxazole-3-carboxylate



[0266] Into a 10 L round-bottom flask, was placed a solution of ethyl 4-cyclopropyl-2,4-dioxobutanoate (177 g) in ethanol (1.1 L) and NH_2OH-HCl (200 g). The resulting solution was stirred for 1 h at 20-30°C. The resulting solution was allowed to react, with stirring, for an additional 1 h at 80°C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1/10). This resulted in 143 g (the two step yield was 66.3%) of ethyl 5-

cyclopropylisoxazole-3-carboxylate as a yellow oil. TLC (ethyl acetate/petroleum ether =1/5): Rf = 0.2.

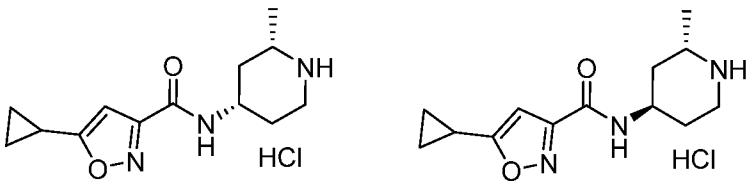
Step 3: Synthesis of 5-cyclopropylisoxazole-3-carboxylic acid



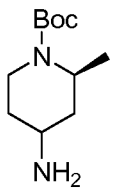
[0267] Into a 10-L round-bottom flask was placed ethyl 5-cyclopropylisoxazole-3-carboxylate (280 g, 1.55 mol, 1.00 equiv) and a solution of sodium hydroxide (74.3 g, 1.20 equiv) in water (4 L). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was washed with ether. The pH value of the aqueous solution was adjusted to 2-3 with hydrochloric acid (12N). The resulting solution was extracted with ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 220 g (93%) of 5-cyclopropylisoxazole-3-carboxylic acid as an off-white solid. LCMS (method A, ESI): RT = 1.99 min, m/z = 153.9 $[M+H]^+$. ^{1}H-NMR (300 MHz $CDCl_3$): 8.42(brs, 1H), 6.37(s, 1H), 2.16-2.05(m, 1H), 1.29-1.12(m, 2H), 1.12-0.99(m, 2H) *ppm*.

EXAMPLE 2

Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride and 5-cyclopropyl-N-((2S,4R)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride



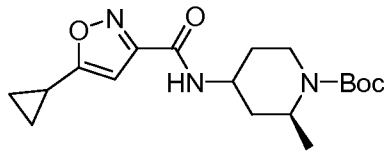
Step 1: Synthesis of (2S)-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate



[0268] Into a 10-L round-bottom flask was placed methanol (5 L), $HCOONH_4$ (190 g, 3.01 mol, 37.80 equiv), acetic acid (5 g, 83.26 mmol, 1.04 equiv) and tert-butyl (2S)-2-methyl-4-oxopiperidine-1-carboxylate (17 g, 79.71 mmol, 1.00 equiv). Then $NaBH_3CN$ (10 g, 159.13 mmol, 2.00 equiv) was added batchwise. The resulting solution was stirred at 25°C overnight. The resulting mixture was concentrated under vacuum. The resulting

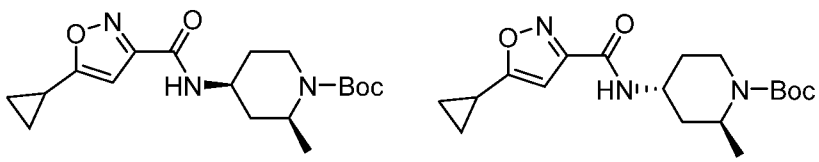
solution was diluted with 500 mL of ethyl acetate. The resulting solution was washed with 3x500 mL of brine (sat.). This resulted in 15.5 g (91%) of tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate as off-white oil. LCMS (method A, ESI): RT=1.21min, *m/z* =215.1 $[M+H]^+$.

Step 2: Synthesis of (2S)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



[0269] Into a 1L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed dichloromethane (500 mL), HOBT (15 g, 111.01 mmol, 1.53 equiv), EDCI (20 g, 104.33 mmol, 1.44 equiv), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (13.3 g, 86.85 mmol, 1.20 equiv) and tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate (15.5 g, 72.33 mmol, 1.00 equiv).Then triethylamine (36 g, 355.77 mmol, 4.92 equiv) was added dropwise. The resulting solution was stirred for 2 hours at 25°C. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 500 mL of ethyl acetate. The resulting mixture was washed with 3x500 mL of water. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 14 g (55%) of tert-butyl (2S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as light yellow oil. LCMS (method A, ESI): RT=2.05 min, *m/z* =350.2 $[M+H]^+$.

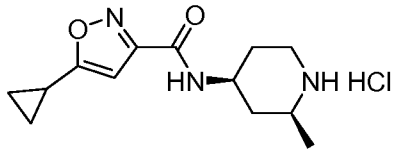
Step 3: Synthesis of tert-butyl (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate and tert-butyl (2S,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate



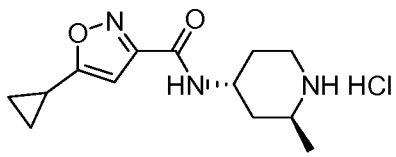
[0270] The crude product was purified by Chrial-HPLC with the following conditions: Column name: CHIRALPAK AD-H, 4.6*150mm,5um,Co-Solvent: EtOH(0.1%DEA), %Co-Solvent: Hexane,25.000, Detector: 220nm. The resulting solution was concentrated under vacuum. This resulted in 9.8 g (70%) of tert-butyl (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as white solid. ^{1}H-NMR (400 MHz,

DMSO): δ 8.54-8.52 (m, 1H), 6.47 (s, 1H), 3.94-3.87(m, 2H), 3.57-3.53(m, 1H), 3.32-3.26(m, 1H), 2.20-2.16(m, 1H), 1.80-1.63(m, 4H), 1.39(s, 9H), 1.16-1.15(m, 3H), 1.10-1.06(m, 2H), 0.93-0.89(m, 2H) *ppm*. And 3.3 g (24%) of tert-butyl (2S,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO): δ 8.54-8.52 (m, 1H), 6.46 (s, 1H), 4.54-4.30(m, 1H), 4.28-4.04(m, 1H), 4.00-3.68(m, 1H), 3.10-2.70(m, 1H), 2.19-2.15(m, 1H), 1.76-1.73(m, 1H), 1.63-1.59(m, 2H), 1.39-1.35(m, 10H), 1.13-1.08(m, 5H),1.00-0.82(m, 2H) *ppm*.

Step 4: Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride and 5-cyclopropyl-N-((2S,4R)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride



[0271] Into a 250-mL round-bottom flask was placed dichloromethane (100 mL), tert-butyl (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (9.8 g, 28.05 mmol, 1.00 equiv). To the above hydrogen chloride was introduced. The resulting solution was stirred for 2 hours at 25°C. The resulting mixture was concentrated under vacuum. This resulted in 8.6 g of 5-cyclopropyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride as a white solid. ^{1}HNMR (400 MHz, MeOD): δ 6.40(s, 1H), 4.24-4.10(m, 1H), 3.55-3.45(m, 1H), 3.40-3.35(m, 1H), 3.19-3.15(m, 1H), 2.24-2.15(m, 3H), 1.82-1.77(m, 1H), 1.63-1.60(m, 1H), 1.93-1.37(m, 3H), 1.21-1.13(m, 2H), 1.00-0.96(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.13 min, *m/z* =250.1 $[M-HCl+H]^+$.

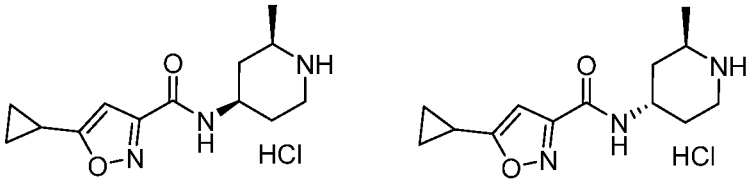


[0272] Into a 100-mL round-bottom flask was placed dichloromethane (50 mL), tert-butyl (2S,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (3.3 g, 9.44 mmol, 1.00 equiv). To the above hydrogen chloride was introduced. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 3 g (crude) of 5-cyclopropyl-N-[(2S,4R)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride as a light yellow solid. ^{1}H NMR (400 MHz, MeOD): δ6.41(s, 1H), 4.36-4.34(m, 1H), 3.62-3.59(m, 1H), 3.40-

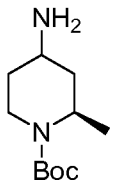
3.35(m, 2H), 2.21-2.03(m, 4H), 1.90-1.82(m, 1H), 1.39-1.37(m, 3H), 1.18-1.14(m, 2H), 1.00-0.96(m,2H) *ppm*. LCMS (method A, ESI): RT=1.03 min, *m/z* =250.1 $[M-HCl+H]^+$.

EXAMPLE 3

Synthesis of 5-cyclopropyl-N-((2R,4R)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride and 5-cyclopropyl-N-((2R,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride

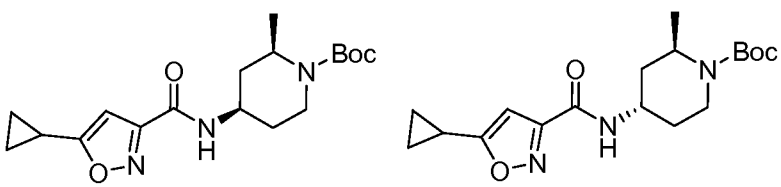


Step 1: Synthesis of (2R)-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate



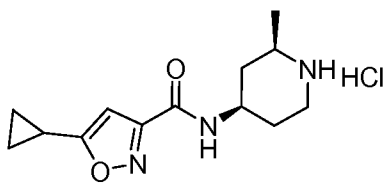
[0273] Into a 5000-mL round-bottom flask was placed tert-butyl (2R)-2-methyl-4-oxopiperidine-1-carboxylate (8.53 g, 40.00 mmol, 1.00 equiv), $HCOONH_4$ (100.8 g, 1.60 mol, 39.97 equiv), methanol (4 L) and acetic acid (2.4 g, 39.97 mmol, 1.00 equiv). Then $NaBH_3CN$ (5.04 g, 80.00 mmol, 2.00 equiv) was added batchwise. The resulting solution was stirred for 15 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 200 mL of brine (sat.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3x100 mL of brine and concentrated under vacuum. This resulted in 10.5 g (98%) of tert-butyl (2R)-4-amino-2-methylpiperidine-1-carboxylate as a white solid. LCMS (method A, ESI): RT=1.06min, *m/z* =159.0 $[M-56+H]^+$. \

Step 2: Synthesis of (2R,4R)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate and (2R,4S)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



[0274] Into a 500-mL round-bottom flask was placed 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (6.12 g, 39.96 mmol, 1.00 equiv), tert-butyl (2R)-4-amino-2-methylpiperidine-1-carboxylate (8.57 g, 39.99 mmol, 1.00 equiv), dichloromethane (300 g), TEA (12.12 g, 120.00 mmol, 3.00 equiv) and HATU (22.8 g, 60.00 mmol, 1.50 equiv). The resulting solution was stirred for 15 h at room temperature. The resulting mixture was then washed with 2x100mL of Na_2CO_3 (1M, aq.). Then the organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (C18 gel, CH_3CN/H_2O = 1:1) to give 10.8 g diastereomeric tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate. Then the purified product was separated by Prep-SFC with the following conditions (prep SFC 350): Column, CHIRALPAK AD-H SFC, 5x25cm,5um; mobile phase, CO_2(50%), methanol(50%); Detector, uv 220nm. This was resulted in 7.48 g (54%) of tert-butyl (2R,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as light yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.86 (d, J = 6.9 Hz, 1H), 6.33 (s, 1H), 4.30-4.15 (m, 2H), 3.93-3.80(m, 1H), 3.22-3.07(m, 1H), 2.20-1.90 (m, 3H), 1.79-1.65(m, 2H), 1.46(s, 9H), 1.26(d, J = 6.9 Hz, 3H), 1.17-1.06(m, 2H), 1.06-0.94(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.46 min, *m/z* =372.2 $[M+H]^+$. And 2.52 g (18%) of tert-butyl (2R,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as a light yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.55 (d, J = 8.1 Hz, 1H), 6.33 (s, 1H), 4.63-4.39 (m, 1H), 4.39-4.15(m, 1H), 4.15-3.95(m, 1H), 3.0-2.85 (m, 1H), 2.15-1.98(m, 2H), 1.92-1.78(m, 1H), 1.65-1.50 (m, 1H), 1.46(s, 9H), 1.42-1.26 (m, 1H), 1.23(d, J = 6.9 Hz, 3H), 1.17-1.06(m, 2H), 1.06-0.94(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.46 min, *m/z* =372.2 $[M+H]^+$.

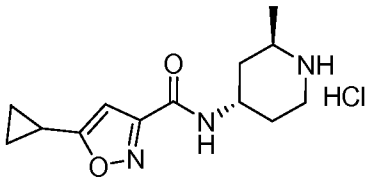
Step 3: Synthesis of 5-cyclopropyl-N-((2R,4R)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride



[0275] Into a 250-mL round-bottom flask was placed tert-butyl (2R,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (7.48 g, 21.41 mmol, 1.00 equiv) and 1,4-dioxane (50 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred for 15 h at room temperature. The resulting

mixture was concentrated under vacuum. This resulted in 6.03 g (99%) of 5-cyclopropyl-N-[(2R,4R)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride as a white solid. LCMS (method D, ESI): RT=0.58 min, *m/z* =250.0 $[M+H]^+$.

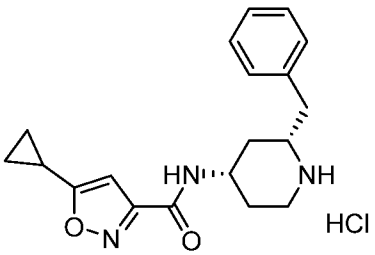
Step 4: Synthesis of 5-cyclopropyl-N-((2R,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride



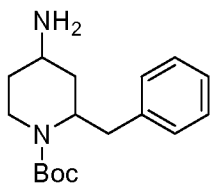
[0276] Into a 100-mL round-bottom flask was placed tert-butyl (2R,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (2.52 g, 7.21 mmol, 1.00 equiv) and 1,4-dioxane (15 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred for 15 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 2.0 g (97%) of 5-cyclopropyl-N-[(2R,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride as a light yellow solid. LCMS (method A, ESI): RT=1.12 min, *m/z* =250.0 $[M+H]^+$.

EXAMPLE 4

Synthesis of N-((2S,4S)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride salt



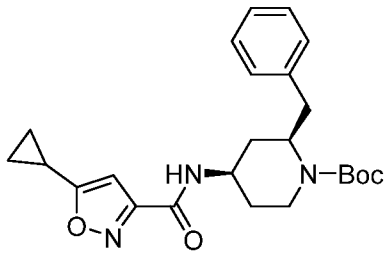
Step 1: Synthesis of tert-butyl 4-amino-2-benzylpiperidine-1-carboxylate



[0277] Into a 5-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl 2-benzyl-4-oxopiperidine-1-carboxylate (5 g, 17.28 mmol, 1.00 equiv), methanol (4 L), acetic acid (2.076 g, 34.57 mmol, 2.00 equiv) and $HCOONH_4$ (43.599 g). The resulting solution was stirred for 0.5 h at room temperature.

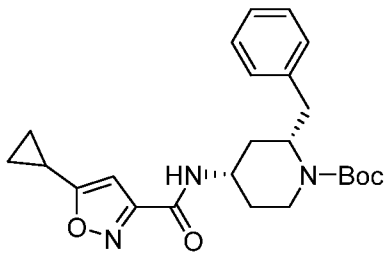
Then $NaBH_3CN$ (2.180 g, 34.69 mmol, 2.01 equiv) was added by batchwise. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 200 mL of EA. The resulting mixture was washed with 4x100 mL of brine (sat.). The organic phase was collected and concentrated under vacuum. The solid was dried in an oven under reduced pressure. This resulted in 5 g (100%) of tert-butyl 4-amino-2-benzylpiperidine-1-carboxylate as light yellow oil. LCMS (method C, ESI): RT =0.89 min, m/z =235.0 $[M-56+H]^+$.

Step 2: Synthesis of (2R,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate



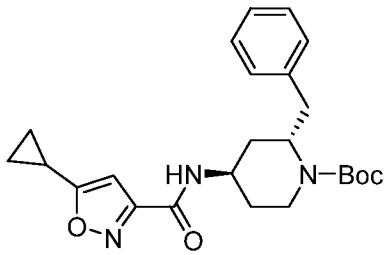
;

(2S,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate



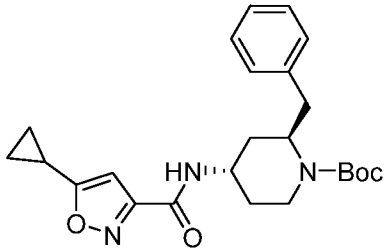
;

(2S,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate



; and

(2R,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate



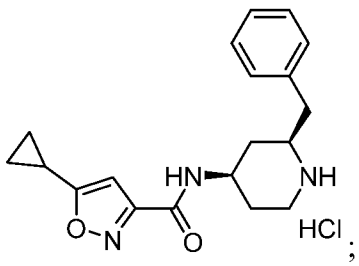
[0278] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl 4-amino-2-benzylpiperidine-1-carboxylate (5 g, 17.22 mmol, 1.00 equiv), dichloromethane (100 mL), TEA (8.707 g, 86.05 mmol, 5.00 equiv), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (3.957 g, 25.84 mmol, 1.50 equiv), HATU (19.655 g, 51.69 mmol, 3.00 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 200 mL of EA. The resulting mixture was washed with 3x200 mL of brine (sat.). The organic phase was collected and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). The collected fractions were combined and concentrated under vacuum. The crude product 2.9 g was purified by Prep-SFC with the following conditions (prep SFC 350-2): Column, Chiralpak AD-H, 5x25cm, 5um; mobile phase, CO_2(70%), IPA(30%) and DCM/MeOH=1/3:100 ; Detector, uv 210nm yielding two fractions: first peak - cis enantiomers 1.7 g, second peak trans enantiomers 0.6 g.

[0279] These products were further purified by SFC. The cis mixtures were purified by Prep-SFC with the following conditions (prep SFC 350-2): Column, Chiralpak AS-H, 5*25cm, 5um; mobile phase, CO_2 (70%), IPA (30%) and MeOH (50%); Detector, uv 210nm. This resulted in 820 mg of (2R,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate as yellow oil and 870 mg of(2S,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate as yellow oil. (2R,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate: ^{1}H-NMR (300 MHz, CD_3Cl) δ: 7.26-7.17(m, 5H), 6.88 (d, J = 6.9 Hz, 1H), 6.32(d, J = 0.6 Hz, 1H), 4.38-4.28 (m, 1H), 4.27-4.16 (m, 1H), 4.09-3.98(m, 1H), 3.18-2.99 (m, 2H), 2.82-2.75 (m,1H), 2.12-1.98(m, 2H), 1.91-1.66 (m, 3H), 1.37(d, J = 2.7 Hz, 9H), 1.18-1.09 (m, 2H), 1.02-0.92 (m, 2H) *ppm*. LCMS (method A, ESI): RT =1.59 min, m/z =326.0 $[M\text{-Boc}+H]^+$. (2S,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate: ^{1}H-NMR (300 MHz,

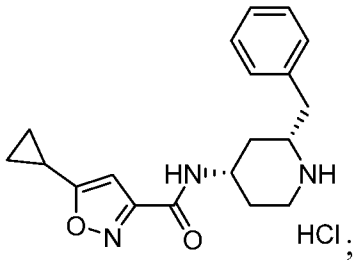
CD_3Cl) δ: 7.26-7.17(m, 5H), 6.88(d, *J* = 6.9 Hz, 1H), 6.32(d, *J* = 0.6Hz, 1H), 4.38-4.28 (m, 1H), 4.27-4.16 (m, 1H), 4.09-3.98(m, 1H), 3.18-2.99 (m, 2H), 2.82-2.75 (m, 1H), 2.12-1.98(m, 2H), 1.91-1.66 (m, 3H), 1.37(d, *J* = 2.7 Hz, 9H), 1.18-1.09(m, 2H), 1.02-0.92(m, 2H) *ppm*. LCMS (method A, ESI): RT =1.59 min, m/z = 326.0 $[M\text{-}Boc+H]^+$.

[0280] The trans mixture was purified by Prep-SFC with the following conditions (prep SFC 350): Column, Phenomenex Lux 5u Cellulose-4250*50mm00G-4491-V0-AX664184-1; mobile phase, CO_2(50%) and MeOH(50%) ,Detector, uv 220 nm. This resulted in 250 mg of (2S,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate as yellow oil and 260 mg of (2R,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate as yellow oil. (2S,4R)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate: ^{1}H-NMR (300 MHz, CD_3Cl) δ: 7.26-7.17(m, 5H), 6.88(d, *J* = 6.9 Hz, 1H), 6.32(s, 1H), 4.81-3.91 (m, 3H), 3.08(t, *J* = 13.5 Hz, 1H), 2.96-2.81(m, 2H), 2.11-2.02(m, 2H), 1.95(d, *J* = 10.5 Hz, 1H), 1.52-1.22(m, 11H), 1.15-1.05(m, 2H), 1.02-0.92(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.58 min, m/z = 448.0 $[M+Na]^+$. (2R,4S)-tert-butyl 2-benzyl-4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate: ^{1}H-NMR (300 MHz, CD_3Cl) δ: 7.26-7.17(m, 5H), 6.88(d, *J* = 6.9 Hz, 1H), 6.32(s, 1H), 4.81-3.91 (m, 3H), 3.08(t, *J* = 13.5 Hz, 1H), 2.96-2.81(m, 2H), 2.11-2.02(m, 2H), 1.95(d, *J* = 10.5 Hz, 1H), 1.52-1.22(m, 11H), 1.15-1.05(m, 2H), 1.02-0.92(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.58 min, m/z = 448.0 $[M+Na]^+$.

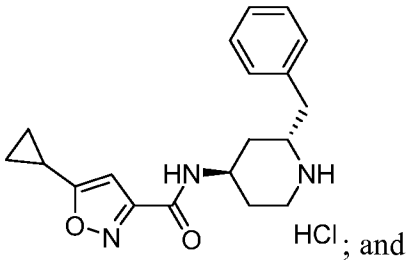
Step 3: Synthesis of N-((2R,4R)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



N-((2S,4S)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride

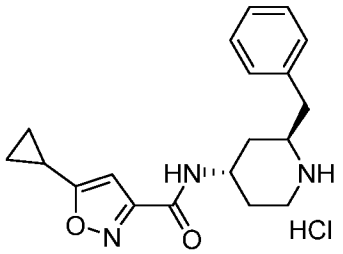


N-((2S,4R)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



; and

N-((2R,4S)-2-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



[0281] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl (2R,4R)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidine-1-carboxylate (820 mg, 1.93 mmol, 1.00 equiv) and 1,4-dioxane (20 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 670 mg (96%) of N-[(2R,4R)-2-benzylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. LCMS (method A, ESI): RT = 1.11 min, m/z = 326.0 $[M+H]^+$.

[0282] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl (2S,4S)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidine-1-carboxylate (870 mg, 2.05 mmol, 1.00 equiv) and 1,4-dioxane (20 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 710 mg (96%) of N-[(2S,4S)-2-

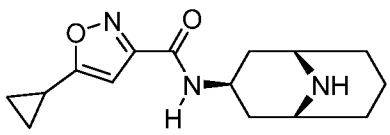
benzylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. LCMS (method A, ESI): RT = 1.10 min, m/z = 326.0 $[M+H]^+$.

[0283] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl (2S,4R)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidine-1-carboxylate (250 mg, 0.59 mmol, 1.00 equiv) and 1,4-dioxane (10 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 190 mg (91%) of N-[(2S,4R)-2-benzylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. LCMS (method A, ESI): RT = 1.11 min, m/z = 326.0 $[M+H]^+$.

[0284] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed tert-butyl (2R,4S)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidine-1-carboxylate (260 mg, 0.61 mmol, 1.00 equiv) and 1,4-dioxane (10 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 200 mg (91%) of N-[(2R,4S)-2-benzylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. LCMS (method A, ESI): RT = 1.11 min, m/z = 326.0 $[M+H]^+$.

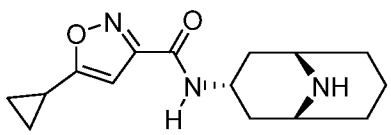
EXAMPLE 5

Synthesis of N-((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide

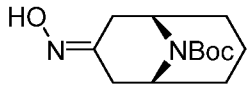


; and

N-((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide

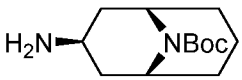


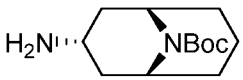
Step 1: Synthesis of (1R,5S,E)-tert-butyl 3-(hydroxyimino)-9-azabicyclo[3.3.1]nonane-9-carboxylate



[0285] Into a 2000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of (1R,5S)-tert-butyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (25 g, 104.03 mmol, 1.00 equiv) in ethanol (500 mL) at room temperature. This was followed by the addition of hydroxylamine hydrochloride (14.5 g, 208.66 mmol, 2.01 equiv) at room temperature. To this was added a solution of sodium hydroxide (8.4 g, 210.00 mmol, 2.02 equiv) in water (250 mL) by dropwise with stirring at room temperature. The resulting solution was stirred for 8 h at 95°C. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 250 mL of H_2O. The resulting solution was extracted with 3x250 mL of dichloromethane and the organic layers combined. The resulting solution was concentrated under vacuum. This resulted in 26 g (98%) of (1R,5S,E)-tert-butyl 3-(hydroxyimino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as a white solid. ^{1}H NMR (300 MHz, DMSO) δ : 10.40(s, 1H), 4.29(s, 2H), 3.04(d, 1H), 2.44-2.27(m, 2H), 1.99(d, 1H), 1.79-1.58(m, 5H), 1.49-1.45 (m, 1H), 1.41(s, 9H) *ppm*. LCMS (Method D, ESI): RT=1.76 min, *m/z* =240.0 $[M -15+H]^+$.

Step 2: Synthesis of (1R,3s,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate

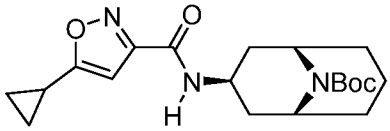


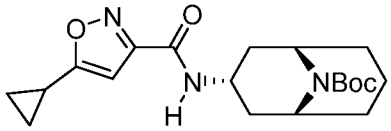


[0286] Into a 5000-mL round-bottom flask was placed a solution of (1R,5S,E)-tert-butyl 3-(hydroxyimino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (26 g, 101.83 mmol, 1.00 equiv) in methanol (4500 mL) at room temperature. This was followed by the addition of Raney-Ni (13 g) at room temperature. The flask was evacuated and flushed three times with nitrogen, then followed by flushing with hydrogen. The mixture was stirred 7h at room temperature under an atmosphere of hydrogen (maintained with 2 atm pressure). The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 21.2 g (86%) of (1R,3s,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.55-4.21(m, 2H), 3.66-3.58(m, 0.27H), 2.73-2.62(m, 0.73H), 2.31-2.18(m, 1H), 2.01-1.89(m, 1H), 1.89-1.75(m, 3H), 1.70-1.52

(m, 3H), 1.52-1.49(m, 1H), 1.46(s, 9H), 1.45-1.35(m, 1.5H), 1.21-1.09(m, 1.5H) *ppm*. LCMS (Method D, ESI): RT=1.28 min, *m/z* =282.0 $[M+H+CH_3CN]^+$.

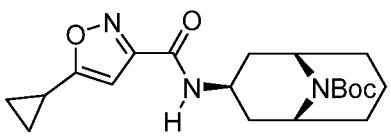
Step 3: Synthesis of (1R,3s,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate

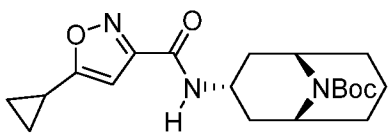




[0287] Into a 1000-mL round-bottom flask was placed (1R,3s,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-amino-9-azabicyclo[3.3.1]nonane-9-carboxylate (20.5 g, 84.94 mmol, 1.00 equiv), dichloromethane (410 mL), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (19.6 g, 127.99 mmol, 1.51 equiv), EDCI (32.6 g, 170.06 mmol, 2.00 equiv), HOBT (17.3 g, 128.03 mmol, 1.51 equiv), TEA (43.1 g, 425.93 mmol, 5.01 equiv). The resulting solution was stirred for 3 h at room temperature. The resulting solution was diluted with 400 mL of DCM. The resulting mixture was washed with 2x400 mL of H_2O. The residue was purified on a silica gel column with dichloromethane/methanol (20:1). This resulted in 30.3 g (95%) of (1R,3s,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ : 6.40(d, 1H), 5.01-4.90(m, 0.33H), 4.55-4.29(m, 2H), 3.92-3.78(m, 0.67H), 2.37-2.21(m, 1.4H), 2.21-1.99(m, 2.6H), 1.95-1.70 (m, 2H), 1.68-1.54(m, 5H), 1.50(s, 9H),1.20-1.10(m, 2H), 1.01-0.91(m, 2H) *ppm*. LCMS (Method D, ESI): RT=2.22 min, *m/z* =361.0 $[M-15+H]^+$.

Step 4: Synthesis of (1R,3s,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate and (1R,3r,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate

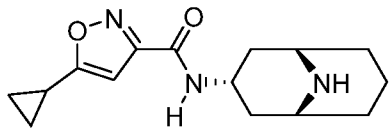




[0288] The mixture of diastereomers (30g) was purified by prep-SFC with the following conditions: Column: Phenomenex Lux 5u Cellulose-35*25cm,5umChiral-P(Lux-3)001608862-1; Detector: UV 220nm; Mobile Phase: CO_2(70%), MeOH(30%). The

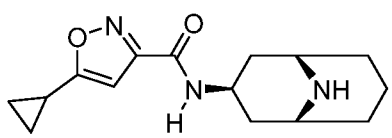
resulting solution was concentrated under vacuum. This resulted in 20.6 g (95%) of (1R,3r,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ : 6.35(s, 1H), 4.47(d, 2H), 3.90-3.75(m, 1H), 2.35-2.23(m, 2H), 2.21-2.02(m, 2H),1.69-1.52(m, 7H), 1.50 (s, 9H), 1.18-1.10(m, 2H), 0.98-0.90(m, 2H) *ppm*. LCMS (Method D, ESI): RT=2.20 min, *m/z* =320.0 $[M-56+H]^+$. And 8.0 g (86%) of (1R,3s,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ : 6.36(s, 1H), 5.02-4.91(m, 1H), 4.34(s, 2H), 2.22-2.10(m, 1H), 2.09-1.97(m, 3H), 1.93-1.64(m, 7H), 1.48 (s, 9H), 1.18-1.10(m, 2H), 0.98-0.90(m, 2H) *ppm*. LCMS (Method D, ESI): RT=2.19 min, *m/z* =320.0 $[M-56+H]^+$.

Step 5: Synthesis of N-((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



[0289] Into a 250-mL round-bottom flask was placed (1R,3r,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate (20.6 g, 54.72 mmol, 1.00 equiv) anddichloromethane (150 mL). To the above hydrogen chloride was introduced. The resulting solution was stirred for 2 h at room temperature. The resulting solution was diluted with 400 mL of H_2O. The pH value of the solution was adjusted to 9 with potassium carbonate. The resulting solution was extracted with 3x250 mL of dichloromethane and the organic layers combined and concentrated under vacuum. This resulted in 14.2 g (94%) of N-((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ : 6.38(s, 1H), 4.29-4.20(m, 1H), 3.36(d, 2H), 2.28-2.11(m, 3H), 2.10-2.00(m, 1H), 1.79-1.69(m, 2H), 1.58-1.37 (m, 5H), 1.19-1.11(m, 2H), 0.98-0.92(m, 2H) *ppm*. LCMS (Method D, ESI): RT=1.23 min, *m/z* =317.0 $[M+H+CH_3CN]^+$.

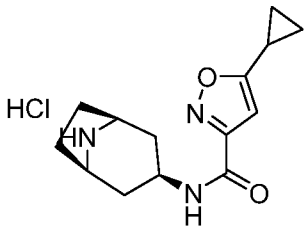
Step 6: Synthesis of N-((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



[0290] Into a 250-mL round-bottom flask was placed (1R,3s,5S)-tert-butyl 3-(5-cyclopropylisoxazole-3-carboxamido)-9-azabicyclo[3.3.1]nonane-9-carboxylate (8.0 g, 21.25 mmol, 1.00 equiv), dichloromethane (100 mL). To the above hydrogen chloride was introduced. The resulting solution was stirred for 2 h at room temperature. The resulting solution was diluted with 300 mL of H_2O. The pH value of the solution was adjusted to 9 with potassium carbonate. The resulting solution was extracted with 3x100 mL of dichloromethane and the organic layers combined and concentrated under vacuum. This resulted in 5.5 g (94%) of N-((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ : 6.38(s, 1H), 4.89-4.80(m, 1H), 3.22(s, 2H), 2.21-2.13(m, 1H), 2.09-1.88(m, 5H),1.85-1.70(m, 5H), 1.19-1.11(m, 2H), 0.98-0.92(m, 2H) *ppm*. LCMS (Method D, ESI): RT=1.20 min, *m/z* =276.0 $[M+H]^+$.

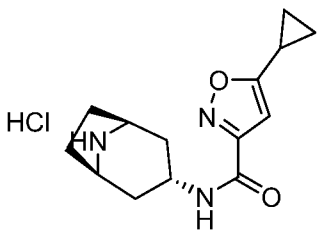
EXAMPLE 6

Synthesis of N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride

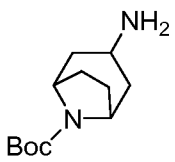


; and

N-((1R,3s,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride

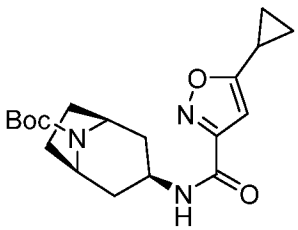


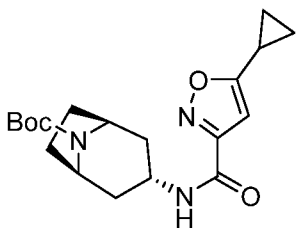
Step 1: Synthesis of tert-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate



[0291] Into a 2000-mL 3-necked round-bottom flask was placed $HCOONH_4$ (42 g, 666.03 mmol, 30.00 equiv), acetic acid (1.3 g, 21.65 mmol, 1.00 equiv) and methanol (1.5 L). Then $NaBH_3CN$ (2.8 g, 44.56mmol, 2.00 equiv) was added into batch wise. This was followed by the addition of a solution of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (5 g, 22.19mmol, 1.00 equiv) in methanol (100mL) dropwise with stirring at 25°C. The resulting solution was stirred for 12 h at 25°C. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 200mL of H_2O. The resulting solution was extracted with 3x200mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x200mL of brine (sat.). The mixture was dried over anhydrous sodium sulfate. The residue was applied onto a silica gel column with dichloromethane/methanol (9:1). This resulted in 4.8 g (90%) of tert-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate as colorless oil. LCMS (method D, ESI): RT=0.97 min, m/z =227.0 $[M+H]^+$.

Step 2: Synthesis of tert-butyl (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,3s,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate

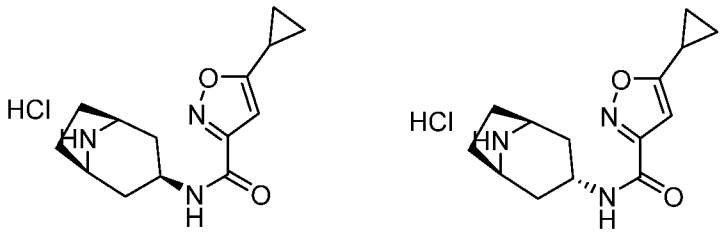




[0292] Into a 250-mL round-bottom flask was placed tert-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (4 g, 17.67mmol, 1.00 equiv), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (2.7 g, 17.63mmol, 1.00 equiv), HATU (10 g, 26.30mmol, 1.50 equiv), DIEA (5.7 g, 44.10mmol, 2.50 equiv), DMF(100mL). The resulting solution was stirred for 12 h at 25°C. The reaction was then quenched by the addition of 100mL of water. The resulting solution was extracted with 3x100mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x100mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:4). The product (4.0g) was further purified by Prep-SFC with the following conditions (prep SFC 350): Column, Phenomenex Lux 5u Cellulose-3, 5*25cm, 5um; mobile phase, CO_2(80%), methanol(20%); Detector, UV220nm. This resulted in 800 mg (13%) of tert-

butyl (1R,3s,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.53 (d, *J=8.0Hz*, 1H), 6.33(s, 1H), 4.41-4.58(m, 1H), 4.24-4.32(m, 2H), 1.95-2.11 (m, 5H), 1.80-1.84(m, 2H), 1.57-1.63(m, 2H), 1.50(s, 9H), 1.16-1.28(m, 2H), 0.95-1.06(m, 2H)*ppm*. LCMS (method D, ESI): RT=2.33 min, *m/z* =362.0 $[M+H]^+$ and 1.4 g (22%) of tert-butyl (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21-7.23(d, *J=7.6Hz*, 1H), 6.34(s, 1H), 4.27-4.33(m, 3H), 2.25-2.31(m, 2H), 2.07-2.14 (m, 3H), 1.91-1.95(m, 2H), 1.76-1.80(m, 2H), 1.49(s, 9H), 1.16-1.28(m, 2H), 0.95-1.06(m, 2H)*ppm*. LCMS (method D, ESI): RT=2.43 min, *m/z* =362.0 $[M+H]^+$.

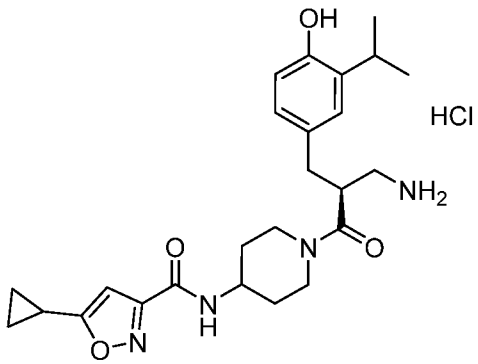
Step 3: Sytnthesis of N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride and N-((1R,3s,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



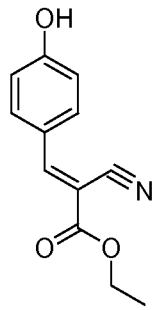
[0293] Into two 50-mL round-bottom flasks was separately placed tert-butyl (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.66mmol, 1.00 equiv) and tert-butyl (1R,3s,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.66mmol, 1.00 equiv). This was followed by the addition of 10 mL of 1,4-dioxane into each flask. Then hydrogen chloride was introduced into the two mixtures. The resulting solutions were stirred for 2 h at 25°C. The resulting mixtures were concentrated under vacuum. This resulted in 480 mg (97%) of N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride LCMS (method D, ESI): RT=0.97 min, m/z =262.0 $[M+H]^+$ and 480 mg (97%) of N-((1R,3s,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride as a light yellow solid. LCMS (method D, ESI): RT=0.95 min, m/z =262.0 $[M+H]^+$.

EXAMPLE 7

Synthesis of N-[1-[(2S)-3-amino-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl] propanoyl]piperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride salt (Cpd. No. 121)

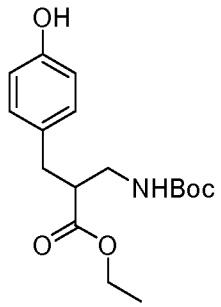


Step 1: Synthesis of ethyl (2E)-2-cyano-3-(4-hydroxyphenyl)prop-2-enoate



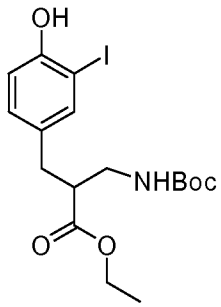
[0294] Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 4-hydroxybenzaldehyde (6 g, 49.13 mmol, 1.00 equiv) and ethanol (200 mL). Then ethyl 2-cyanoacetate (6.7 g, 59.23 mmol, 1.21 equiv) and piperidine (2 mL) was added. The resulting solution was stirred overnight at 90°C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 8.5 g (80%) of ethyl (2E)-2-cyano-3-(4-hydroxyphenyl)prop-2-enoate as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.19(s, 1H), 7.97(d, J=8.7 Hz, 2H), 6.99(d, J=8.7 Hz, 2H), 6.11 (brs, 1H), 4.41-4.31(m, 2H), 1.40(t, J=7.2 Hz, 3H) *ppm*. LCMS (method A, ESI): RT=1.34min, *m/z* =217.9 $[M+H]^+$.

Step 2: Synthesis of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxyphenyl)methyl] propanoate



[0295] Into a 500-mL round-bottom flask was placed ethyl (2E)-2-cyano-3-(4-hydroxyphenyl)prop-2-enoate (8.5 g, 39.13 mmol, 1.00 equiv), methanol (200 mL) and di-tert-butyl dicarbonate (9.4 g, 43.07 mmol, 1.10 equiv). Then Raney-Ni (3 g) was added batchwise. Then H_2 was introduced into mixture and maintained at 2 atm pressure. The resulting solution was stirred overnight at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 12 g (95%) of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxyphenyl)methyl]propanoate as a light yellow solid. LCMS (method C, ESI): RT=0.95 min, *m/z* =324.2 $[M+H]^+$.

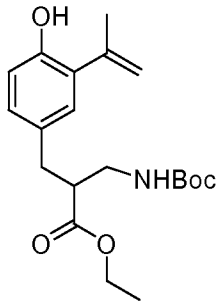
Step 3: Synthesis of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxy-3-iodophenyl)methyl]propanoate



[0296] Into a 250-mL round-bottom flask was placed ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxyphenyl)methyl]propanoate (5 g, 15.46 mmol, 1.00 equiv), TsOH (266 mg, 1.54 mmol, 0.10 equiv) and dichloromethane (80 mL). Then NIS (3.48 g, 15.47 mmol, 1.00 equiv) was added into at room temperature. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 4.2 g (60%) of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxy-3-iodophenyl)methyl]propanoate as a light yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.46(d, J=2.1 Hz, 1H), 7.06-7.02(m, 1H), 6.89(d, J=9.6 Hz, 1H), 4.15-4.07(m, 2H), 3.32-3.24(m, 2H), 2.84-2.72(m, 3H), 1.43(s,

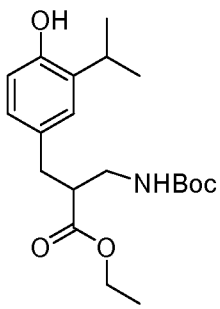
9H), 1.19(t, J=6.9 Hz, 3H) *ppm*. LCMS (method A, ESI): RT=1.70 min, *m/z* =349.9 [M-Boc+H]$^+$.

Step 4: Synthesis of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(prop-1-en-2-yl)phenyl]methyl]propanoate



Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[(4-hydroxy-3-iodophenyl)methyl]propanoate (4 g, 8.90 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (1.8 g, 10.71 mmol, 1.20 equiv), $Pd(dppf)Cl_2$ (650 mg), Cs_2CO_3 (8.7 g, 26.62 mmol, 2.99 equiv), and N,N-dimethylformamide (50 mL). The resulting solution was stirred overnight at 100°C. The resulting solution was diluted with 40 mL of NH_4Cl (sat. aq.). The resulting solution was extracted with 4x40 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 4x50 mL of NH_4Cl (sat. aq.). The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 1 g (31%) of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(prop-1-en-2-yl)phenyl]methyl]propanoate as light brown oil. LCMS (method A, ESI): RT=1.74 min, *m/z* =264.0 [M-Boc+H]$^+$.

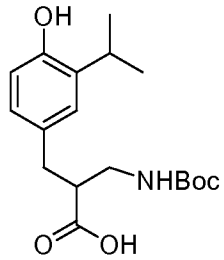
Step 5: Synthesis of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-yl)phenyl]methyl]propanoate



[0297] Into a 250-mL round-bottom flask, was placed ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(prop-1-en-2-yl)phenyl]methyl]propanoate (1.3

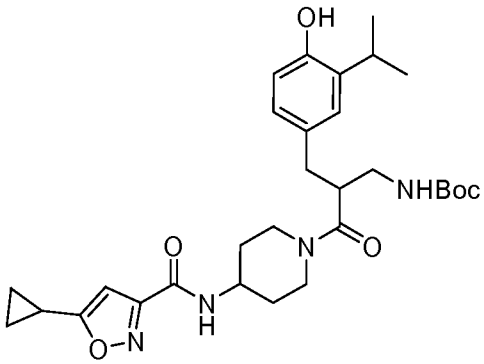
g, 3.58 mmol, 1.00 equiv), ethyl acetate (40 mL) and 10% Palladium carbon (0.7 g). Then H_2 was introduced into mixture and maintained at 2 atm pressure. The resulting solution was stirred overnight at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 1.0 g (76%) of ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]propanoate as light yellow oil. LCMS (method D, ESI): RT=1.57 min, *m/z* =366.0 $[M+H]^+$.

Step 6: Synthesis of 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]propanoic acid



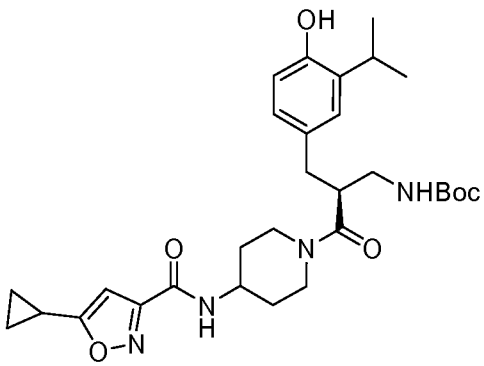
[0298] Into a 250-mL round-bottom flask was placed ethyl 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]propanoate (1 g, 2.74 mmol, 1.00 equiv), ethanol (40 mL), water(0.5 mL), sodium hydroxide (0.45 g). The resulting solution was stirred for 6 h at room temperature. The resulting mixture was concentrated under vacuum. The pH value of the solution was adjusted to 4 with hydrochloric acid (12N). The resulting solution was extracted with 5x30 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 0.6 g (65%) of 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]propanoic acid as colorless oil. LCMS (method A, ESI): RT=1.56 min, *m/z* =360.1 $[M+Na]^+$.

Step 7: Synthesis of tert-butyl N-[3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate



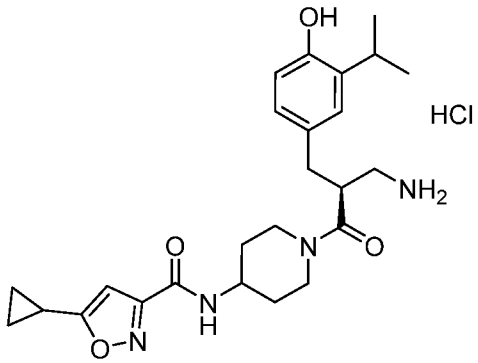
[0299] Into a 250-mL round-bottom flask was placed 3-[[(tert-butoxy)carbonyl]amino]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]propanoic acid (600 mg, 1.78 mmol, 1.00 equiv), 5-cyclopropyl-N-(piperidin-4-yl)-1,2-oxazole-3-carboxamide hydrochloride (750 mg, 2.76 mmol, 1.55 equiv), EDCI (0.85 g), HOBT (0.6 g) and dichloromethane (60 mL). Then TEA (0.9 g) was added into dropwise at 0°C. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:10). The product was further purified by Prep-HPLC with the following conditions (2#-Waters 2767-2(HPLC-08)): Column, Xbridge Prep Phenyl, 5 um, 19x150 mm; mobile phase, Water with 50 mmol ammonium bicarbonate and acetonitrile (10.0% acetonitrile up to 33.0% in 2 min, up to 53.0% in 8 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm. This resulted in 650 mg (66%) of tert-butyl N-[3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate as a white solid. LCMS (method A, ESI): RT=1.69 min, *m/z* =455.2 $[M\text{-Boc }+H]^+$.

Step 8: Synthesis of tert-butyl N-[(2S)-3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate



[0300] The tert-butyl N-[3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate (600 mg, 1.08 mmol, 1.00 equiv) was separated by Chiral-HPLC with following conditions: (Chiral-p(Lux-4)003667995-2): Column, Phenomenex Lux 5u Cellulose-4, AXIA Packed250*21.2 mm,5 um, mobile phase, Phase A: Hex-HPLC and Phase B: EtOH-HPLC Gradient; Detector, uv 254/220 nm. This resulted in 256 mg (43%) of tert-butyl N-[(2S)-3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate as a white solid. LCMS (method A, ESI): RT=1.68 min, *m/z* =455.3 $[M\text{-Boc }+H]^+$.

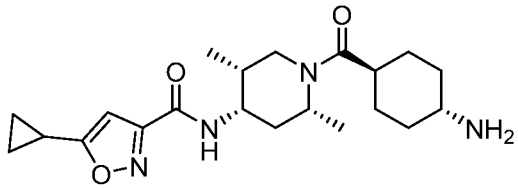
Step 9: Synthesis of N-[1-[(2S)-3-Amino-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl] propanoyl]piperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride salt



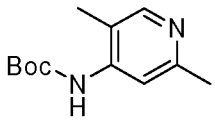
[0301] Into a 100-mL round-bottom flask was placed tert-butyl N-[(2S)-3-[4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl]-3-oxopropyl]carbamate (256 mg, 0.46 mmol, 1.00 equiv) and dichloromethane (20 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred for 4 h at room temperature. The solids were collected by filtration. The resulting filtrate was concentrated under vacuum. This resulted in 152.2 mg (67%) of N-[1-[(2S)-3-amino-2-[[4-hydroxy-3-(propan-2-yl)phenyl]methyl] propanoyl]piperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 6.99(dd, J=20.4 and 2.1 Hz, 1H), 6.86-6.81(m, 1H), 6.73-6.69(m, 1H), 6.36(d, J=0.6 Hz, 1H), 4.60-4.37(m, 1H), 4.05-3.88(m, 1H), 3.87-3.63(m, 1H), 3.50-3.36(m, 1H), 3.30-2.98(m, 3.5H), 2.88-2.72(m, 3H), 2.62-2.45(m, 0.5H), 2.21-2.11(m, 1H), 1.96-1.62(m, 2H), 1.62-1.42(m, 1H), 1.40-1.24(m, 0.5H), 1.23-1.18(m, 6H), 1.18-1.09(m, 2H), 1.02-0.90(m, 2H), 0.78-0.60(m, 0.5H) *ppm*. LCMS (method D, ESI): RT=1.96 min, *m/z* =455.1 $[M+H]^+$. ee=100%.

EXAMPLE 8

Synthesis of N-((2R,4S,5R)-1-((1r,4R)-4-aminocyclohexanecarbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 420)

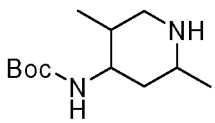


Step 1: Synthesis of tert-butyl 2,5-dimethylpyridin-4-ylcarbamate



[0302] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of 2,5-dimethylpyridin-4-amine (488 mg, 3.99 mmol, 1.00 equiv) in tetrahydrofuran (10 mL), di-tert-butyl dicarbonate (959.2 mg, 4.40 mmol, 1.10 equiv). This was followed by the addition of LiHMDS ((7.98mL, 7.98 mmol, 2.00 equiv, 1M in THF solution) dropwise with stirring at 0°C. The resulting solution was stirred at 25°C overnight. The reaction was then quenched by the addition of 50 mL of NH_4Cl (sat. aq.). The resulting solution was extracted with 3x20 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100:1). This resulted in 740 mg (83%) of tert-butyl 2,5-dimethylpyridin-4-ylcarbamate as yellow oil. LCMS (method C, ESI): RT=0.83min, m/z=223.0 $[M+H]^+$.

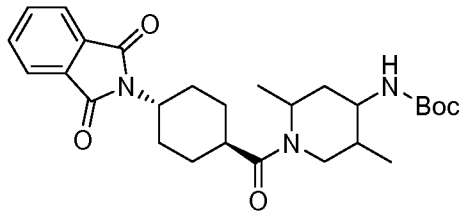
Step 2: Synthesis of tert-butyl 2,5-dimethylpiperidin-4-ylcarbamate



[0303] Into a 30-mL high pressure tank reactor (70 atm), was placed a solution of tert-butyl N-(2,5-dimethylpyridin-4-yl)carbamate (1.11 g, 4.99 mmol, 1.00 equiv) in ethanol (25 mL), and 5% Rh/Al_2O_3. Then hydrogen was introduced into mixture and maintained at 70 atm. The resulting solution was stirred for 2 days at 70°C. The reaction mixture was cooled to 25°C. The solids were filtered out. The resulting mixture was concentrated

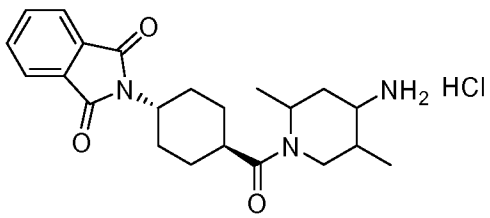
under vacuum. This resulted in 440 mg of tert-butyl 2,5-dimethylpiperidin-4-ylcarbamate as black oil. LCMS (method A, ESI): RT=1.12min, m/z=229.0 $[M+H]^+$.

Step 3: Synthesis of tert-butyl 1-((1R,4R)-4-(1,3-dioxoisoindolin-2-yl)cyclohexanecarbonyl) -2,5-dimethylpiperidin-4-ylcarbamate



[0304] Into a 25-mL round-bottom flask was placed tert-butyl N-(2,5-dimethylpiperidin-4-yl)carbamate (183.7 mg, 0.80 mmol, 1.10 equiv), (1R,4R)-4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclohexane-1-carboxylic acid (200 mg, 0.73 mmol, 1.00 equiv), HATU (334 mg, 0.88 mmol, 1.20 equiv). This was followed by the addition of TEA (370 mg, 3.66 mmol, 5.00 equiv) by dropwise with stirring. The resulting solution was stirred for 16 hours at 25°C. The resulting solution was diluted with 100 mL of dichloromethane. The resulting mixture was washed with 3x30 mL of brine (sat. aq.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100:1). This resulted in 700 mg of tert-butyl 1-((1R,4R)-4-(1,3-dioxoisoindolin-2-yl)cyclohexanecarbonyl)-2,5-dimethylpiperidin-4-ylcarbamate as yellow oil. LCMS (method D, ESI): RT=0.91min, m/z=484.0 $[M+H]^+$.

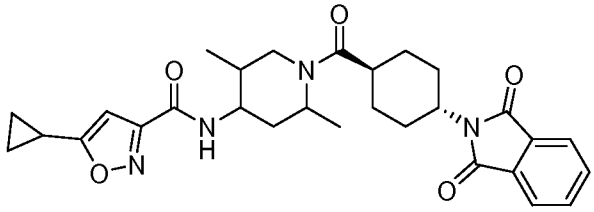
Step 4: Synthesis of 2-((1R,4R)-4-(4-Amino-2,5-dimethylpiperidine-1-carbonyl)cyclohexyl) isoindoline-1,3-dione hydrochloride



[0305] Into a 100-mL round-bottom flask was placed a solution of tert-butyl N-(2,5-dimethyl-1-[[(1R,4R)-4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclohexyl]carbonyl]piperidin-4-yl)carbamate (700 mg, 1.45 mmol, 1.00 equiv) in dichloromethane (30 mL). To the above hydrogen chloride was introduced. The resulting solution was stirred for 30 min at 25°C. The resulting mixture was concentrated under vacuum. This resulted in 490 mg of 2-((1R,4R)-4-(4-amino-2,5-dimethylpiperidine-1-

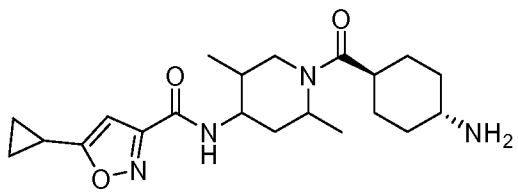
carbonyl)cyclohexyl)isoindoline-1,3-dione hydrochloride as yellow oil. LCMS (method C, ESI): RT=1.11 min, m/z=384.0[M+H]$^+$.

Step 5: Synthesis of 5-Cyclopropyl-N-(1-((1R,4R)-4-(1,3-dioxoisoindolin-2-yl)cyclohexanecarbonyl)-2,5-dimethylpiperidin-4-yl)isoxazole-3-carboxamide



[0306] Into a 100-mL round-bottom flask was placed 2-[(1R,4R)-4-[(4-amino-2,5-dimethylpiperidin-1-yl)carbonyl]cyclohexyl]-2,3-dihydro-1H-isoindole-1,3-dione (838 mg, 2.19 mmol, 1.10 equiv), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (306 mg, 2.00 mmol, 1.00 equiv), HATU (912 mg, 2.40 mmol, 1.20 equiv). This was followed by the addition of triethylamine (1 g, 9.88 mmol, 5.00 equiv) dropwise with stirring. The resulting solution was stirred at 25°C overnight. The resulting solution was diluted with 100 mL of dichloromethane. The resulting mixture was washed with 3x30 mL of brine (sat.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100:1). This resulted in 500 mg of 5-cyclopropyl-N-(2,5-dimethyl-1-[[(1R,4R)-4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclohexyl]carbonyl]piperidin-4-yl)-1,2-oxazole-3-carboxamide as yellow oil. LCMS (method C, ESI): RT=0.99 min, m/z=519.0[M+H]$^+$

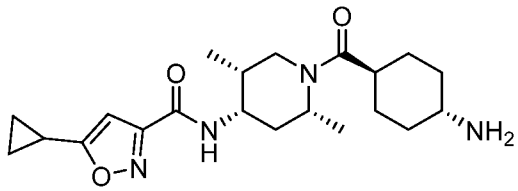
Step 6: Synthesis of N-(1-((1R,4R)-4-Aminocyclohexanecarbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0307] Into a 100-mL round-bottom flask was placed 5-cyclopropyl-N-(2,5-dimethyl-1-[[(1R,4R)-4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclohexyl]carbonyl]piperidin-4-yl)-1,2-oxazole-3-carboxamide (518 mg, 1.00 mmol, 1.00 equiv), water (1 mL) and propan-2-ol (6 mL). Then $NaBH_4$ (380 mg, 10.05 mmol, 10.00 equiv) was added batchwise. The resulting solution was stirred for 16 hours at 25°C. This was followed by the addition of acetic acid (0.2 mL, 0.10 equiv) dropwise with stirring. The resulting solution was allowed to react with stirring for 2 hour while the temperature was

maintained at 80°C in an oil bath. Then the reaction system was cooled. The pH value of the solution was adjusted to 8 with sodium carbonate (50 %, aq.). The resulting solution was extracted with 3x15 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100:1). This resulted in 72.9 mg (19%) of 5-cyclopropyl-N-(2,5-dimethyl-1-[[(1R,4R)-4-aminocyclohexyl]carbonyl]piperidin-4-yl)-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 6.40(s, 1 H), 4.89-3.70 (m, 3 H), 3.32-2.68(m, 3H), 2.27-2.09(m, 4 H), 1.95-1.90 (m, 4 H), 1.68-1.47(m, 4 H), 1.34-1.11(m, 5 H), 0.92-1.01(m, 5 H) *ppm*. LCMS (method A, ESI): RT=1.32 min, m/z=389.0[M+H]$^+$.

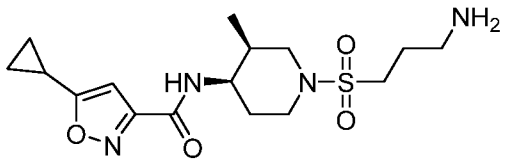
Step 7: Synthesis of N-((2R,4S,5R)-1-((1r,4R)-4-Aminocyclohexanecarbonyl)-2,5-dimethylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



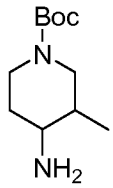
[0308] The crude product was purified by Chrial-HPLC with the following conditions: Column, SHIMADZU-PDA(LC-08) ; mobile phase, Hex (0.2%IPA) : EtOH=70:30; Detector, UV 254/220 nm. This resulted in 9.6 mg (24%) of (2S,4R,5S)-benzyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2,5-dimethylpiperidine-1-carboxylate as a white solid and 9.3 mg (23%) of (2R,4S,5R)-benzyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2,5-dimethylpiperidine-1-carboxylate was obtained as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 6.30(s, 1 H), 4.76-3.60 (m, 3 H), 3.10-2.90(m, 1 H), 2.85-2.75(m, 1 H), 2.61-2.45(m, 1H), 2.10-2.03(m, 2 H), 1.93-1.73 (m, 6 H), 1.57-1.31(m, 2 H), 1.31-1.02(m, 7 H), 0.89-0.84(m, 5 H) *ppm*. LCMS (method A, ESI): RT=1.31 min, m/z=389.0[M+H]$^+$.

EXAMPLE 9

Synthesis of N-((3S,4R)-1-(3-aminopropylsulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 386)

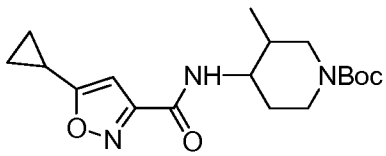


Step 1: Synthesis of tert-butyl 4-amino-3-methylpiperidine-1-carboxylate



[0309] Into a 4-L round-bottom flask was placed methanol (3 L), formic acid (0.5 mL), $HCOONH_4$ (84 g, 1.33 mol, 40.00 equiv) and tert-butyl 3-methyl-4-oxopiperidine-1-carboxylate (7 g, 32.82 mmol, 1.00 equiv).Then $NaBH_3CN$ (4.1 g, 2.00 equiv) was added into batchwise. The resulting solution was stirred for 2 hours at room temperature. The pH value of the solution was adjusted to 9 with sodium carbonate (5M in water). The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 50 mL of H_2O. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined. This resulted in 7.0 g (99% crude) of tert-butyl 4-amino-3-methylpiperidine-1-carboxylate as a white solid. ^1H NMR (300 MHz, DMSO): 6.39(brs, 2H), 3.95-3.75(m, 1.5H), 3.70-3.60(m, 0.5H), 3.35-3.25(brs, 0.5H), 3.05-2.95(m, 0.5H), 2.90-2.63(m, 1.5H), 2.45-2.25(brs, 0.5H), 2.10-2.00 (brs, 0.5H), 1.95-1.85(m, 0.5H), 1.65-1.45(m, 1.5H), 1.35-1.25(m, 0.5H), 1.38(s, 9H), 1.20-1.10(m, 3H) *ppm*. LCMS (Method A, ESI): RT=1.02 min, m/z =215.0 $[M+H]^+$.

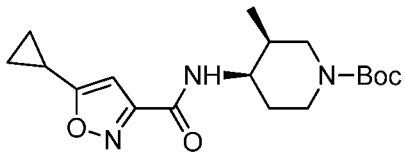
Step 2: Synthesis of tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylate



[0310] Into a 250-mL round-bottom flask was placed tert-butyl 4-amino-3-methylpiperidine-1-carboxylate (7 g, 32.66 mmol, 1.00 equiv), dichloromethane (100 mL), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (6.5 g, 42.45 mmol, 1.30 equiv), HATU (25.1 g, 104.13 mmol, 2.00 equiv). Then TEA (16.7 g, 165.04 mmol, 5.00 equiv) was added into mixture dropwise. The resulting solution was stirred for 2 h at room temperature. The resulting solution was concentrated under vacuum. The resulting solution was diluted with 50 mL of H_2O. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3x150 mL of brine (sat.). The mixture was dried over anhydrous sodium sulfate. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1/5). This

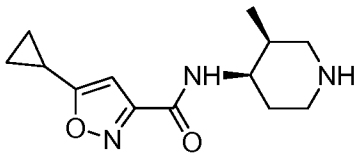
resulted in 6 g (52%) of tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylateas yellow solid. ^{1}H NMR (400 MHz, CD_3OD) : 6.38(s, 1H), 4.30-4.20(m, 1H), 4.20-4.05(m, 1H), 3.80-3.76(m, 1H), 3.56-3.45 (m, 1H), 3.29-3.20 (m, 1H), 2.15-2.10(m, 2H), 1.90-1.80(m, 1H), 1.70-1.60(m, 1H), 1.52(s, 9H), 1.20-1.16(m, 2H), 1.05-0.85(m, 5H) *ppm*. LCMS (Method A, ESI): RT=1.47 min, m/z =294.0 $[M+H-56]^+$.

Step 3: Synthesis of (3S,4R)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylate



[0311] 1.5g of tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylatewas purified by Chrial-Prep-SFC with the following conditions: Column: CHIRALCEL OJ-3 (0.46*15cm,3um); mobile phase, Hex:EtOH=90:10; Detector, 254nm. This resulted in 240 mg (16%) of (3S,4R)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylateas a white solid. ^{1}H NMR (400 MHz, CD_3OD) : 6.40(s, 1H), 4.25-4.22(m, 1H), 4.00-3.88(brs, 1H), 3.77-3.55(brs, 1H), 3.24-3.23(m, 2H), 2.20-2.15 (m, 2H), 1.85-1.81(m, 1H), 1.67-1.64(m, 1H) , 1.48(s, 9H) 1.17-1.16(m, 2H), 1.05-0.98(m, 5H) *ppm*.

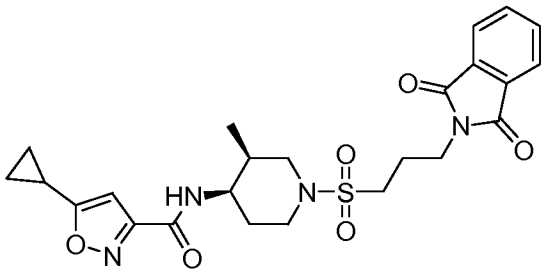
Step 4: Synthesis of 5-cyclopropyl-N-((3S,4R)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide



[0312] Into a 100-mL round-bottom flask was placed (3S,4R)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-3-methylpiperidine-1-carboxylate (240 mg, 0.688 mmol, 1.00 equiv), dichloromethane (30 mL). To the above hydrogen chloride was introduced. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 10 mL of water. The pH value of the solution was adjusted to 9 with sodium carbonate (5M in water). The resulting solution was extracted with 3x10 mL of ethyl acetate and the organic layers combined. This resulted in 150 mg (71%) of 5-cyclopropyl-N-[(3S,4R)-3-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. 1H NMR (400 MHz,

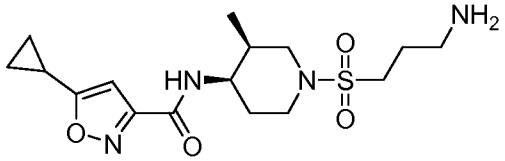
CD_3OD) : 6.40(s, 1H), 4.28-4.26(m, 1H), 3.05-2.90(brs, 1H), 2.90-2.70(m, 3H), 2.20-2.05 (m, 2H), 1.90-1.70(m, 2H), 1.20-1.10(m, 2H) , 1.05-0.95(m, 5H) *ppm*. LCMS (Method A, ESI): RT=0.97 min, m/z =250.0 [M+H].

Step 5: Synthesis of 5-cyclopropyl-N-((3S,4R)-1-(3-(1,3-dioxoisoindolin-2-yl)propylsulfonyl)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide



[0313] Into a 25-mL round-bottom flask was placed 5-cyclopropyl-N-((3S,4R)-3-methylpiperidin-4-yl)isoxazole-3-carboxamide (150 mg, 0.60 mmol, 1.00 equiv), dichloromethane (20 mL) and TEA (180 mg, 3.00 equiv). Then 3-(1,3-dioxo-2,3-dihydro-1H-inden-2-yl)propane-1-sulfonyl chloride (207 mg, 0.72 mmol, 1.30 equiv) was added into the mixture dropwise at-20°C. The resulting solution was stirred for additional 24 hours at -20°C. The resulting mixture was concentrated under vacuum. The resulting mixture was triturated with 3x10 mL of EA. The solids were collected by filtration. This resulted in 300 mg (100%) of 5-cyclopropyl-N-[(3S,4R)-1-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-3-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. LCMS (method A, ESI): RT=1.40 min, *m/z* =501.0 [M+H].

Step 6: Synthesis of N-((3S,4R)-1-(3-aminopropylsulfonyl)-3-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide

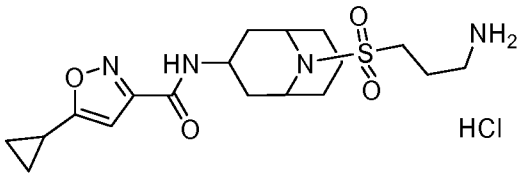


[0314] Into a 25-mL round-bottom flask was placed 5-cyclopropyl-N-[(3S,4R)-1-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-3-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide (300 mg, 0.60 mmol, 1.00 equiv), methanol (10 mL) and hydrazine hydrate (1 mL, 80% in water). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by Prep-HPLC with the following conditions : Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A:Water/NH_4HCO_3 10mmol, Mobile

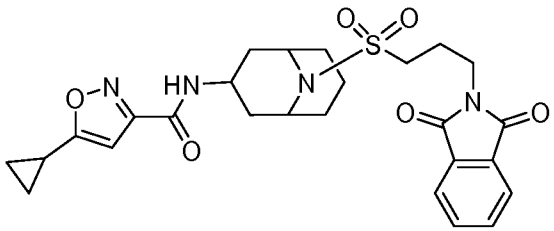
Phase B: ACN; Flow rate: 30 mL/min; Gradient: 30%B to 85%B in 10 min; Detector,254nm This resulted in 66.4 mg (30%) of N-[(3R,4S)-1-[(3-aminopropane)sulfonyl]-3-methylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ : 6.40(s, 1H), 4.24-4.20(m, 1H), 3.61-3.57(m, 1H), 3.50-3.32(m, 1H), 3.25-3.08(m, 4H), 2.85- 2.75 (m, 2H), 2.30-2.14(m, 2H), 2.00-1.89(m, 3H), 1.80-1.70(m, 1H), 1.20-1.15(m, 2H), 1.10-0.95(m, 5H) *ppm*. LCMS (Method D, ESI): RT=2.11 min, *m/z* =371.0 $[M+H]^+$.

EXAMPLE 10

Synthesis of N-[9-[(3-aminopropane)sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride salt (Cpd. No. 181



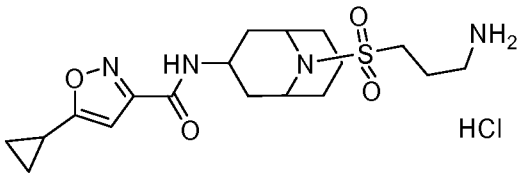
Step 1: Synthesis of 5-cyclopropyl-N-(9-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl)-1,2-oxazole-3-carboxamide



[0315] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of argon was placed N-[9-azabicyclo[3.3.1]nonan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide (250 mg, 0.91 mmol, 1.00 equiv), tetrahydrofuran (20 mL), the solution was cooled to -30°C, then LiHMDS (3 mL) was added and stirred for 30 min at -30°C, and a solution of 3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane-1-sulfonyl chloride (340 mg, 1.18 mmol, 1.30 equiv) in tetrahydrofuran (3 mL) was added slowly. The resulting solution was stirred overnight at room temperature. The resulting solution was diluted with 10 mL of ethyl acetate. The solids were filtered out. The resulting filtrate was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 200 mg (42%) of 5-cyclopropyl-N-(9-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl)-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (400

MHz, $CDCl_3$): δ 8.50 (d, J=8.0 Hz, 1H), 7.89-7.82 (m, 4H), 6.47 (s, 1H), 4.78-4.77(m, 1H), 4.00-3.98(m, 2H), 3.70(t, J=7.2 Hz, 2H), 3.20(t, J=7.2 Hz, 2H), 2.20-2.16(m, 1H), 2.01-1.97(m, 2H), 1.87-1.81(m, 7H), 1.68(d, J=8.4 Hz, 3H), 1.13-1.06 (m, 2H), 0.93-0.89 (m, 2H) *ppm*. LCMS (method D, ESI): RT=1.48min, *m/z* =527.1 $[M+H]^+$.

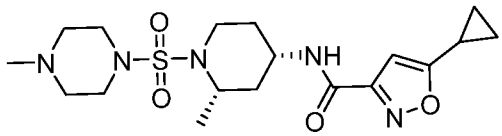
Step 2: Synthesis of N-[9-[(3-aminopropane)sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride salt



[0316] Into a 250-mL round-bottom flask, was placed 5-cyclopropyl-N-(9-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl)-1,2-oxazole-3-carboxamide (200 mg, 0.38 mmol, 1.00 equiv), methanol (30 mL)and hydrazine hydrate (4 mL). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate. The crude product (200 mg) was further purified by Prep-HPLC with the following conditions: Column, X Bridge C18, 19*150 mm, 5 um; mobile phase, Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Detector, 254 nm. This resulted in 118.7 mg (72%) of N-[9-[(3-aminopropane)sulfonyl]-9-azabicyclo[3.3.1]nonan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 6.40 (s, 1H), 5.04-4.89 (m, 1H), 4.14 (brs, 2H), 3.24 (t, J=7.5 Hz, 2H), 3.13 (t, J=7.8 Hz, 2H), 2.20-1.77 (m, 13H), 1.17-1.12 (m, 2H), 0.99-0.94(m, 2H) *ppm*. LCMS (method D, ESI): RT=1.35 min, *m/z* =397.0 $[M+H]^+$.

EXAMPLE 11

Synthesis of 5-cyclopropyl-N-[(2S,4S)-2-methyl-1-(4-methylpiperazine-1-sulfonyl) piperidin-4-yl]-1,2-oxazole-3-carboxamide (Cpd. No. 279)

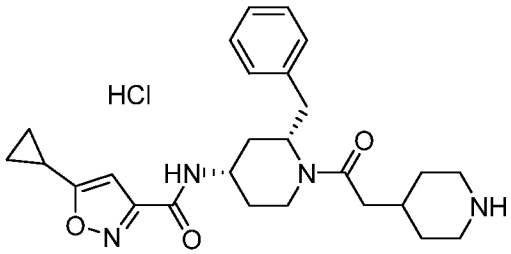


[0317] Into a 50-mL 3-necked round-bottom flask was placed 5-cyclopropyl-N-((2S,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride (200 mg, 0.70 mmol,

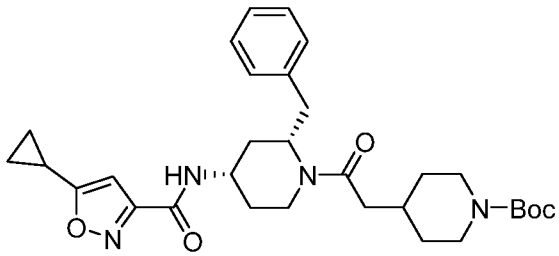
1.00 equiv), dichloromethane (10 mL) and TEA (353 mg, 3.49 mmol, 4.98 equiv). This was followed by the addition of 4-methylpiperazine-1-sulfonyl chloride (166 mg, 0.84 mmol, 1.19 equiv) at -20°C. The resulting solution was stirred at room temperature overnight. The reaction progress was monitored by LCMS. The resulting mixture was washed with 2x5 mL of H_2O. The residue was purified on a silica gel column with dichloromethane/methanol (20:1). This resulted in 136.3 mg (47%) of 5-cyclopropyl-N-[(2S,4S)-2-methyl-1-(4-methylpiperazine-1-sulfonyl)piperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ : 6.37(s, 1H), 4.14-4.11(m, 1H), 3.76-3.63(m, 2H), 3.27-3.24(m, 1H), 3.21(t, 4H), 2.51(t, 4H), 2.32 (s, 3H), 2.19-2.13(m, 1H), 2.01-1.95(m, 2H), 1.85-1.65(m, 2H), 1.41(d, 3H), 1.17-1.10(m, 2H), 0.99-0.94(m, 2H) *ppm*. LCMS (Method D, ESI): RT=1.74 min, *m/z* =412.0 $[M+H]^+$.

EXAMPLE 12

Synthesis of N-((2S,4S)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (Cpd. No. 348)



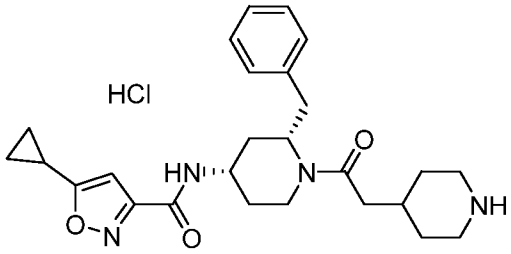
Step 1: Synthesis of tert-butyl 4-[2-[(2S,4S)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxylate



[0318] Into a 250-mL round-bottom flask was placed *N*-[(*2S,4S*)-2-benzylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide (100 mg, 0.31 mmol, 1.00 equiv), dichloromethane (50 mL), HATU (353 mg, 0.93 mmol, 3.02 equiv), TEA (157 mg, 1.55 mmol, 5.05 equiv), 2-[1-[(tert-butoxy)carbonyl]piperidin-4-yl]acetic acid (75 mg, 0.31 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature. The

resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 130 mg (77%) of tert-butyl 4-[2-[(2S,4S)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxylate as a yellow solid. LCMS (method A, ESI) : RT=1.13 min. m/z = 451.0 $[M\text{-}Boc]^+$.

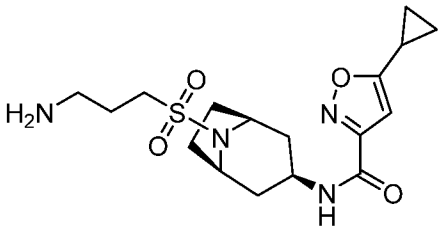
Step 2: Synthesis of N-((2S,4S)-2-benzyl-1-(2-(piperidin-4-yl)acetyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



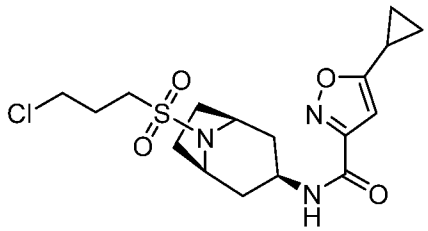
[0319] Into a 100-mL round-bottom flask was placed tert-butyl 4-[2-[(*2S,4S*)-2-benzyl-4-(5-cyclopropyl-1,2-oxazole-3-amido)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxylate (130 mg, 0.24 mmol, 1.00 equiv) and 1,4-dioxane (20 mL). Then hydrogen chloride was introduced into mixture. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 64.0 mg (56%) of *N*-[(2S,4S)-2-benzyl-1-[2-(piperidin-4-yl)acetyl]piperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride as a white solid. ^1H NMR (400 MHz, D_2O): δ : 7.22-7.06 (m, 5H), 6.30 (s, 1H), 4.70 (s, 0.5H), 4.38-4.30 (m, 0.5H), 4.30-4.15 (m, 0.5H), 4.15-3.95 (m, 1H), 3.75-3.65(m, 0.5H), 3.65-3.45 (m, 0.5H), 3.30-3.01 (m, 3H), 3.01-2.90 (m, 0.5H), 2.90-2.70 (m, 3H), 2.45-2.35 (m, 0.5H), 2.20-2.01 (m, 2H), 2.01-1.81 (m, 4H), 1.81-1.65 (m, 1.5H), 1.65-1.51 (m, 1H), 1.51-1.41 (m, 1H), 1.41-1.39 (m, 1.5H), 1.10-1.01 (m, 2H), 0.98-0.83 (m, 2.5H) *ppm*. LCMS (method D, ESI): RT=1.98 min. m/z = 451.0 $[M\text{-}HCl]^+$.

EXAMPLE 13

Synthesis of N-((1S,3r,5R)-8-(3-aminopropylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 485)

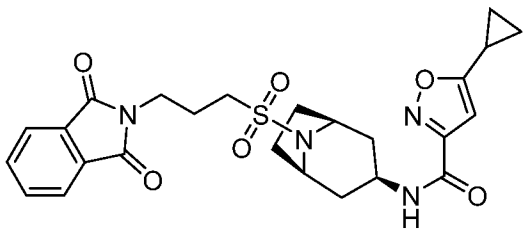


Step 1: Synthesis of N-((1R,3r,5S)-8-(3-chloropropylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



[0320] Into a 25-mL round-bottom flask was placed N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide (200 mg, 0.62mmol, 1.00 equiv), dichloromethane (5mL), TEA (189 mg, 1.87mmol, 3.00 equiv). This was followed by the added of 3-chloropropane-1-sulfonyl chloride (143 mg, 0.81mmol, 1.30 equiv) dropwise at 0°C. The resulting solution was stirred overnight at 25°C. The solution was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 240 mg (96%) of N-[(1R,3r5S)-8-[(3-chloropropane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide as yellow oil. LCMS (method D, ESI): RT=0.97min, m/z =402.0 $[M+H]^+$.

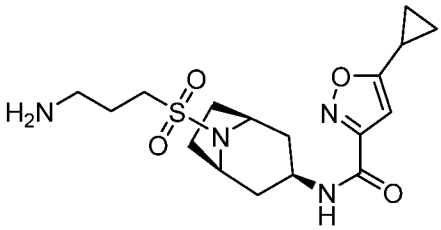
Step 2: Synthesis of 5-cyclopropyl-N-((1S,3r,5R)-8-(3-(1,3-dioxoisoindolin-2-yl)propylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide



[0321] Into a 25-mL round-bottom flask was placed N-[(1R,3S,5S)-8-[(3-chloropropane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide (100 mg, 0.25mmol, 1.00 equiv), N,N-dimethylformamide (5 mL), 2-potassio-2,3-dihydro-1H-isoindole-1,3-dione (92 mg, 0.50mmol, 2.00 equiv). The resulting solution was stirred for 2 h at 80°C. The resulting solution was extracted with

3x50 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3x70 mL of water. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 120 mg (94%) of 5-cyclopropyl-N-[(1R,3r,5S)-8-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide as a white solid. LCMS (method D, ESI): RT=0.98 min, *m/z* =513.0 $[M+H]^+$.

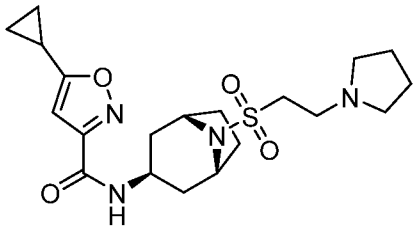
Step 3: Synthesis of N-((1S,3r,5R)-8-(3-aminopropylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



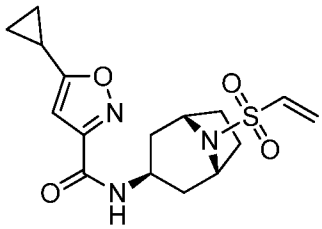
[0322] Into a 25-mL round-bottom flask was placed 5-cyclopropyl-N-[(1R,3r,5S)-8-[[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propane]sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide (120 mg, 0.23mmol, 1.00 equiv) and $N_2H_4.H_2O$ (0.2 mL), methanol (7 mL). The resulting solution was stirred for 4 h at 25°C. The mixture was concentrated under vacuum and then dissolved in 50mL ethyl acetate. The solids were filtered out. The filtrate was concentrated under vacuum. The crude product (100mg) was purified by Prep-HPLC with the following conditions(1#-Waters 2767-1): Column, X-bridge Prep phenyl 5um,19*150mmh Prep C012(T)186003581138241113.01; mobile phase, Phase A:water with 0.5% NH_4HCO_3 ,Phase B:CH_3CN .Water with 0.5% NH_4HCO_3 and CH_3CN (30% CH_3CN up to 60% in 12 min ,hold 95% in 1min ,down to 30% in 1 min); Detector, uv254nm. This resulted in 50.7 mg (57%) of N-[(1R,3r,5S)-8-[(3-aminopropane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide as a white solid. ^1H NMR (400 MHz, CD_3OD): 6.28 (s, 1H), 4.13 (s, 2H), 4.07-4.04 (m, 1H), 3.07-3.03 (m, 2H), 2.69-2.66 (m, 2H), 2.21-2.15(m, 2H), 2.08-1.80 (m, 9H), 1.06-1.01 (m, 2H), 0.89-0.85 (m, 2H) *ppm*. LCMS (method D, ESI): RT=1.30 min, *m/z* =383.0 $[M+H]^+$.

EXAMPLE 14

Synthesis of 5-cyclopropyl-N-((1R,3s,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (Cpd. No. 436

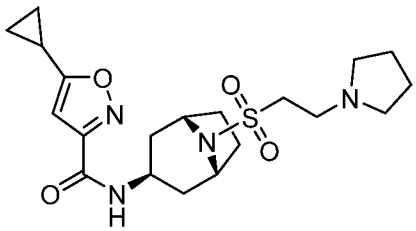


Step 1: Synthesis of 5-cyclopropyl-N-((1R,3s,5S)-8-(vinylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide



[0323] Into a 50-mL round-bottom flask was placed N-[(1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride (100 mg, 0.34 mmol, 1.00 equiv), TEA (102 mg, 1.01 mmol, 3.00 equiv), dichloromethane (5 mL). This was followed by the dropwise addition of ethenesulfonyl chloride (61 mg, 0.48 mmol, 1.30 equiv) at 0°C. Then the resulting solution was stirred for 2 h at 25°C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (3:1). This resulted in 100 mg (85%) of 5-cyclopropyl-N-[(1R,3s,5S)-8-(ethenesulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide as a light brown solid. LCMS (method D, ESI): RT=0.59 min, *m/z* =383.1 $[M+Na]^+$.

Step 2: Synthesis of 5-cyclopropyl-N-((1R,3s,5S)-8-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide

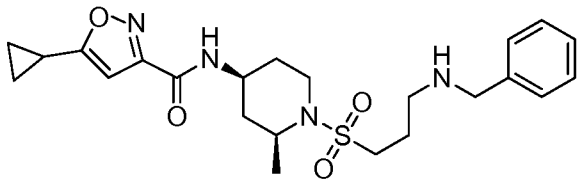


[0324] Into a 50-mL round-bottom flask was placed 5-cyclopropyl-N-[(1R,3s,5S)-8-(ethenesulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide (90 mg, 0.26mmol, 1.00 equiv), ethanol (10 mL), and pyrrolidine (0.2 mL). The resulting solution was stirred at 25°C overnight. The resulting mixture was concentrated under vacuum. The crude product (89mg) was purified by Prep-HPLC with the following conditions(1#-

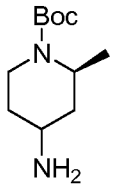
Waters 2767-1): Column, X-bridge Prep phenyl 5um,19*150mmh Prep C012(T)186003581138241113.01; mobile phase, Phase A:water with 0.5% NH_4HCO_3 ,Phase B:CH_3CN .Water with 0.5% NH_4HCO_3 and CH_3CN (80% CH_3CN up to 95% in 13 min ,hold 95% in 1min ,down to 80% in 1 min); Detector, uv254nm. This resulted in 60.3 mg (56%) of 5-cyclopropyl-N-[(1R,3s,5S)-8-[[2-(pyrrolidin-1-yl)ethane]sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ6.27 (s, 1H), 4.21-4.11 (m, 2H), 4.02-4.08 (m, 1H), 3.22-3.18 (m, 2H), 2.84-2.79 (m, 2H), 2.52-2.49 (m, 4H), 2.19-2.14 (m, 2H), 2.08-1.72 (m, 11H), 1.06-1.01 (m, 2H), 0.89-0.85 (m, 2H) *ppm*. LCMS (method D, ESI): RT=1.36 min, *m/z* =423 $[M+H]^+$.

EXAMPLE 15

Synthesis of N-((2S,4S)-1-(3-(benzylamino)propylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 500)

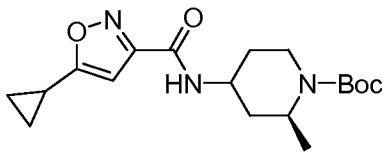


Step 1: Synthesis of (2S)-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate



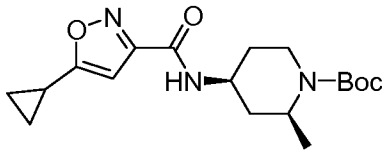
[0325] Into a 10-L round-bottom flask was placed methanol (5 L), $HCOONH_4$ (190 g, 3.01 mol, 37.80 equiv), acetic acid (5 g, 83.26 mmol, 1.04 equiv) and tert-butyl (2S)-2-methyl-4-oxopiperidine-1-carboxylate (17 g, 79.71 mmol, 1.00 equiv). Then $NaBH_3CN$ (10 g, 159.13 mmol, 2.00 equiv) was added into the mixture slowly. The resulting solution was stirred overnight at 25°C. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 500 mL of ethyl acetate. The resulting mixture was washed with 3x500 mL of brine (sat.). The resulting organic phase was concentrated under vacuum. This resulted in 15.5 g (91%) of tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate as off-white oil. LCMS (method A, ESI): RT=1.21min, *m/z* =215.1 $[M+H]^+$.

Step 2: Synthesis of (2S)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



[0326] Into a 1L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed dichloromethane (500 mL), HOBT (15 g, 111.01 mmol, 1.53 equiv), EDCI (20 g, 104.33 mmol, 1.44 equiv), 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (13.3 g, 86.85 mmol, 1.20 equiv) and tert-butyl (2S)-4-amino-2-methylpiperidine-1-carboxylate (15.5 g, 72.33 mmol, 1.00 equiv). Then triethylamine (36 g, 355.77 mmol, 4.92 equiv) was added dropwise. The resulting solution was stirred for 2 hours at 25°C. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 500 mL of ethyl acetate. The resulting mixture was washed with 3x500 mL of water. The resulting organic phase was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 14 g (55%) of tert-butyl (2S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as light yellow oil. LCMS (method A, ESI): RT=2.05 min, *m/z* =350.2 $[M+H]^+$.

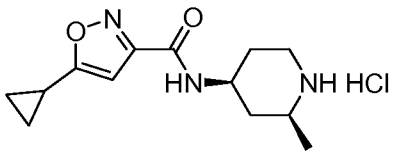
Step 3: Synthesis of (2S,4S)-tert-butyl 4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-carboxylate



[0327] The diastereomeric product was further purified by Chiral-HPLC with the following conditions: Column name: CHIRALPAK AD-H, 4.6*150mm,5um,Co-Solvent: EtOH(0.1%DEA), %Co-Solvent: Hexane,25.000, Detector: 220nm. The resulting solution was concentrated under vacuum. This resulted in 9.8 g (70%) of tert-butyl (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as colorless oil. ^{1}H-NMR (400 MHz, DMSO): δ 8.54-8.52 (m, 1H), 6.47 (s, 1H), 3.94-3.87(m, 2H), 3.57-3.53(m, 1H), 3.32-3.26(m, 1H), 2.20-2.16(m, 1H), 1.80-1.63(m, 4H), 1.39(s, 9H), 1.16-1.15(m, 3H), 1.10-1.06(m, 2H), 0.93-0.89(m, 2H) *ppm* and 3.3 g (24%) of tert-butyl (2S,4R)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO): δ 8.54-8.52 (m, 1H),

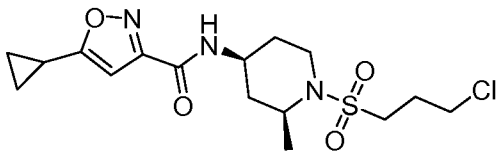
6.46 (s, 1H), 4.54-4.30(m, 1H), 4.28-4.04(m, 1H), 4.00-3.68(m, 1H), 3.10-2.70(m, 1H), 2.19-2.15(m, 1H), 1.76-1.73(m, 1H), 1.63-1.59(m, 2H), 1.39-1.35(m, 10H), 1.13-1.08(m, 5H), 1.00-0.82(m, 2H) *ppm*.

Step 4: Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride



[0328] Into a 250-mL round-bottom flask was placed dichloromethane (100 mL) and tert-butyl (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (9.8 g, 28.05 mmol, 1.00 equiv). To the above hydrogen chloride (gas) was introduced into mixture. The resulting solution was stirred for 2 hours at 25°C. The resulting mixture was concentrated under vacuum. This resulted in 8.6 g of 5-cyclopropyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride as a white solid. ^{1}HNMR (400 MHz, MeOD): δ 6.40(s, 1H), 4.24-4.10(m, 1H), 3.55-3.45(m, 1H), 3.40-3.35(m, 1H), 3.19-3.15(m, 1H), 2.24-2.15(m, 3H), 1.82-1.77(m, 1H), 1.63-1.60(m, 1H),1.93-1.37(m, 3H), 1.21-1.13(m, 2H), 1.00-0.96(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.13 min, *m/z* =250.1 $[M-HCl+H]^+$.

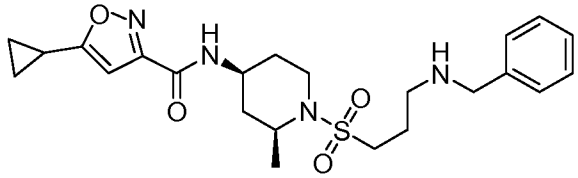
Step 5: Synthesis of N-((2S,4S)-1-(3-chloropropylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0329] Into a 25-mL round-bottom flask was placed dichloromethane (5 mL), triethylamine (121 mg, 1.20 mmol, 2.98 equiv) and 5-cyclopropyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide (100 mg, 0.40 mmol, 1.00 equiv). Then 3-chloropropane-1-sulfonyl chloride (106 mg, 0.60 mmol, 1.49 equiv) was added dropwise at 0°C. The resulting solution was stirred for 16 hours at 25°C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/hexane (1:1). This resulted in 85 mg (54%) of N-[(2S,4S)-1-[(3-chloropropane)sulfonyl]-2-methylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 6.38(s, 1H), 4.13-4.01

(m, 1H), 3.80-3.72 (m, 3H), 3.66-3.65 (m, 1H), 3.26-3.19 (m, 3H), 2.19-2.00 (m, 3H), 2.04-1.98 (m, 2H), 1.77-1.70 (m, 2H), 1.43 (d, *J=6.8Hz*, 3H), 1.00-0.97 (m, 2H) , 1.16-1.12 (m, 2H)*ppm*. LCMS (method A, ESI): RT=1.37min, *m/z* =390.0 $[M+H]^+$.

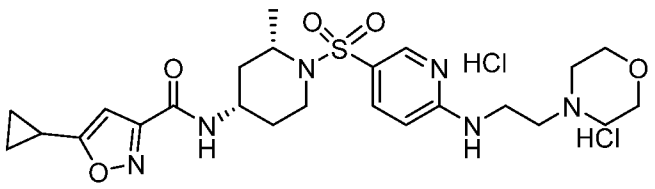
Step 6: Synthesis of N-((2S,4S)-1-(3-(benzylamino)propylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



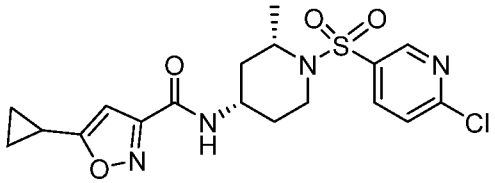
[0330] Into a 10mL round-bottom flask was placed 1,4-dioxane (3mL), N-[(2S,4S)-1-[(3-chloropropane)sulfonyl]-2-methylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide (84 mg, 0.22 mmol, 1.00 equiv), and phenylmethanamine (274 mg, 2.56 mmol, 11.87 equiv). The resulting solution was stirred for 16 hours at 100°C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/hexane (1:1). This resulted in 30.1 mg (30%) of N-[(2S,4S)-1-[[3-(benzylamino)propane]sulfonyl]-2-methylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.37-7.29 (m, 5H), 6.38(s, 1H), 4.13-4.01 (m, 1H), 3.82(s, 2H), 3.80-3.78 (m, 1H), 3.62 (d, *J=3.2Hz*, 1H), 3.18-3.11(m, 3H), 2.78 (t, *J=3.2Hz,* 2H), 2.18-2.16 (m, 1H), 2.04-1.97 (m, 4H), 1.77-1.70 (m, 2H), 1.43 (d, *J=6.8Hz*, 3H), 1.00-0.97 (m, 2H), 1.16-1.12 (m, 2H) *ppm*. LCMS (method A, ESI): RT=1.48min, *m/z* =461.3 $[M+H]^+$.

EXAMPLE 16

Synthesis of 5-cyclopropyl-N-((*2S,4S*)-2-methyl-1-(6-(2-morpholinoethylamino) pyridin-3-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide dihydrochloride (Cpd. No. 458)

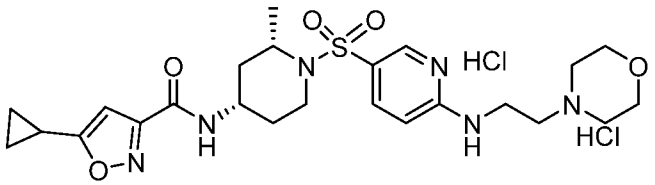


Step 1: Synthesis of N-((2S,4S)-1-(6-chloropyridin-3-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0331] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-cyclopropyl-N-((2S,4S)-2-methylpiperidin-4-yl)isoxazole-3-carboxamide hydrochloride (200 mg, 0.69 mmol, 1.00 equiv). Then triethylamine (210 mg, 2.09mmol, 3.00 equiv) was added into dropwsie. The reaction mixture was cooled to 0 °C, then 6-chloropyridine-3-sulfonyl chloride (220 mg, 1.04 mmol, 1.50 equiv) was added dropwise. The resulting solution was stirred at room temperature for 15 h. The resulting mixture was washed by water (3x10ml), dried over Na_2SO_4 and concentrated under vacuum. This resulted in 296 mg (97%) of *N*-((*2S,4S*)-1-(6-chloropyridin-3-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide as light yellow solid. LCMS (method D, ESI): RT=1.47min, *m/z* =425 $[M+H]^+$.

Step 2: Synthesis of 5-cyclopropyl-*N*-((*2S,4S*)-2-methyl-1-(6-(2-morpholinoethylamino) pyridin-3-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide dihydrochloride



[0332] Into a 50-mL round-bottom flask was placed *N*-((*2S,4S*)-1-(6-chloropyridin-3-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (296 mg, 0.69 mmol, 1.00 equiv), 2-morpholinoethanamine (226 mg, 1.74 mmol, 2.4 equiv) and 1,4-dioxane (5 mL). The resulting solution was stirred at 80°C for 15 h. The resulting mixture was purified by pre-HPLC. Column: X Select C18, 19x150 mm, 5 um; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 5%B to 45%B in 11.5 min; 254nm. This resulting eluent was acidified by hydrochloric acid (6Nand concentrated resulting in 102.80 mg (28%) of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-(6-(2-morpholinoethylamino)pyridin-3-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide dihydrochloride as light yellow solid. ^{1}H-NMR (300 MHz, D_2O): δ 8.44 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.29(s, 1H), 4.14-3.08 (m, 16H), 2.12-2.08 (m, 1H), 1.97-1.86 (m, 2H), 1.64-1.79 (m, 2H), 1.26-1.24 (d, *J* = 6.0 Hz, 3H),

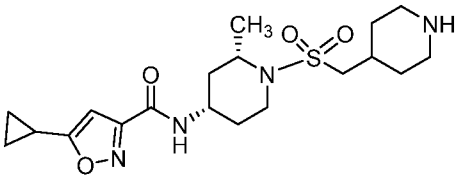
1.08-1.05(m, 2H), 0.99-0.74(m, 2H) *ppm*. LCMS (method D, ESI): RT=2.37 min, *m/z* =519.0 $[M+H]^+$.

EXAMPLE 17

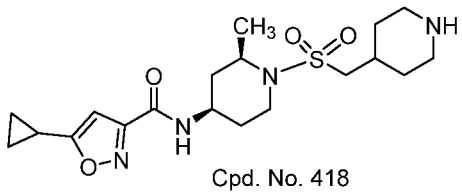
Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (Cpd. No. 417)

and

5-cyclopropyl-N-((2R,4R)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (Cpd. No. 418)

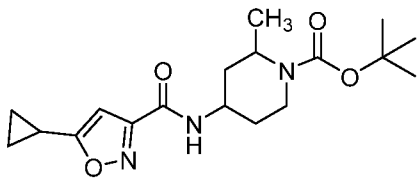


Cpd. No. 417



Cpd. No. 418

Step 1: Synthesis of tert-butyl 4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate

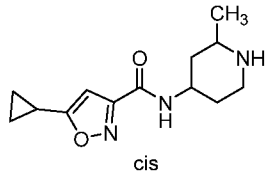


cis

[0333] To a solution of cis tert-butyl 4-amino-2-methylpiperidine-1-carboxylate (1 g, 4.67 mmol) and DIPEA (2.44 ml, 14 mmol) in DMF (25ml) was added 5-cyclopropyl-1,2-oxazole-3-carboxylic acid (0.86 g, 5.6 mmol) followed by HATU (2.31 g, 6.07 mmol). The reaction was stirred at rt. LCMS analysis after ~1h showed a trace of SM and mainly product (72%, 1.33min, MNa+.=371.95). The reaction was poured into water (100ml) and the product was extracted with EtOAc (3x50ml). The combined organic layers were washed with water (2x50ml), brine (50ml), dried over Na_2SO_4, filtered and concentrated. The red oily residue was purified by Isolera over SiO_2 (100g), eluting with a gradient of EtOAc in heptane from 5 to 50 % to yield 1.55 g (95%) of the amide as an amber viscous. TLC (25% EtOAc in Hept), rf:0.30. ^{1}H NMR (500 MHz, Chloroform-d) δ 6.85 (d, J = 6.8 Hz, 1H), 6.31 (s, 1H), 4.21 (hept, J = 6.8, 6.1 Hz, 2H), 3.85 (ddd, J = 14.0, 5.5, 3.1 Hz, 1H), 3.13 (ddd, J = 14.3, 11.9, 3.9 Hz, 1H), 2.06 (ddd, J = 8.4, 4.9, 3.4 Hz, 1H), 2.02 – 1.91 (m, 2H), 1.74 – 1.66 (m, 2H), 1.45 (s, 9H), 1.25 (d, J = 7.2 Hz, 3H),

1.13 – 1.08 (m, 2H), 1.00 – 0.94 (m, 2H). LCMS analysis (METCR1673 Generic 2 minutes), 100%, 1.33min, $[MNa]^{+}$=372.00.

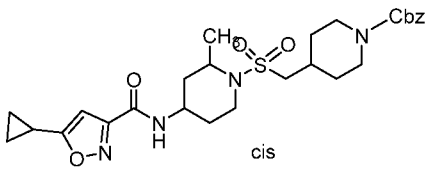
Step 2: Synthesis of 5-cyclopropyl-N-(2-methylpiperidin-4-yl)-1,2-oxazole-3-carboxamide hydrochloride



cis

[0334] A solution of tert-butyl 4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-carboxylate (1.55 g, 4.44 mmol) in DCM (50ml) was treated with 4M HCl in dioxane (15 ml) at rt for ~4h. LCMS analysis showed complete reaction. The solvent was evaporated to dryness to yield 1.12 g (88%) of the amine as HCl salt as a white solid. ^{1}H NMR (250 MHz, Methanol-d4) δ 6.38 (s, 1H), 4.17 (tt, J = 11.9, 4.1 Hz, 1H), 3.53 – 3.34 (m, 2H), 3.14 (td, J = 13.3, 3.1 Hz, 1H), 2.28 – 2.08 (m, 3H), 1.94 – 1.52 (m, 2H), 1.37 (d, J = 6.5 Hz, 3H), 1.20 – 1.09 (m, 2H), 1.00 – 0.91 (m, 2H). LCMS analysis (METCR1673 Generic 2 minutes), 100%, ~0.45 min, $[MH\text{-}HCl]^{+}$=250.00.

Step 3: Synthesis of benzyl 4-({[4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidin-1-yl]sulfonyl}methyl)piperidine-1-carboxylate

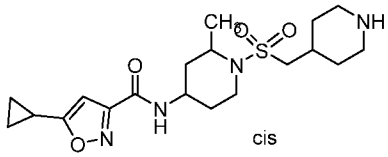


cis

[0335] To a solution of 5-cyclopropyl-N-(2-methylpiperidin-4-yl)-1,2-oxazole-3-carboxamide hydrochloride (920 mg, 3.22 mmol) in DCM (40ml) was added DIPEA (3.37ml, 19.3 mmol) followed by benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (1175 mg, 3.54 mmol) as a solution in DCM (10ml) and the reaction was left at rt overnight. The reaction was diluted with DCM (100ml) and washed with water (50ml) and brine (50ml). The combined aqueous layers were back-extracted with EtOAc (2x25ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by Isolera over SiO_2 (100g), dry loaded and eluted with a gradient of EtOAc in heptane from 12 to 100% then with a gradient of MeOH in EtOAc from 0 to 20% to yield 0.92 g (47%) of sulfonamide as a white solid. TLC (2.5% MeOH in DCM), rf:0.30. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.40 – 7.28 (m, 5H), 6.77 (d, J = 7.4 Hz, 1H), 6.32 (s, 1H), 5.12 (s, 2H), 4.20 (ddt, J = 16.0, 7.7, 4.5 Hz, 3H),

3.76 – 3.63 (m, 2H), 3.21 (ddd, J = 13.5, 7.4, 3.8 Hz, 1H), 2.83 (hept, J = 6.4 Hz, 4H), 2.24 – 1.90 (m, 6H), 1.79 – 1.69 (m, 2H), 1.44 (d, J = 6.9 Hz, 3H), 1.33 – 1.22 (m, 2H), 1.16 – 1.09 (m, 2H), 1.01 – 0.96 (m, 2H). LCMS analysis (METCR1673 Generic 2 minutes), 100%, 1.38 min, $[MH]^{+}$=545.00.

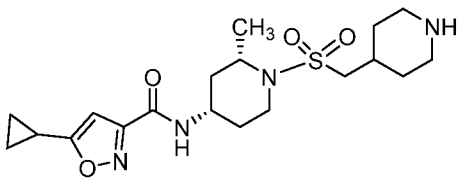
Step 4: Synthesis of 5-cyclopropyl-N-[2-methyl-1-(piperidin-4-ylmethanesulfonyl) piperidin-4-yl]-1,2-oxazole-3-carboxamide



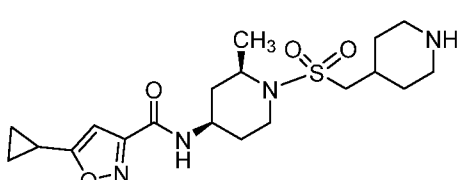
cis

[0336] To a solution of benzyl 4-({[4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidin-1-yl]sulfonyl}methyl)piperidine-1-carboxylate (90%, 917 mg, 1.52 mmol) in MeCN (50ml) and DCM (5ml) was added TMS-I (647 µl, 4.55 mmol) at rt for 1h. The solution was then added onto 50ml of 0.5M HCl in MeOH and the mixture was stirred at rt for an additional ~2h. The solvent was evaporated and the residue was purified by Isolute SCX-2 (10g cartridge) eluted with MeOH (15x10ml) then with 7N NH_3 in MeOH to yield 636 mg (96%) of 5-cyclopropyl-N-(2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide as a white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 6.79 (d, J = 7.2 Hz, 1H), 6.32 (s, 1H), 4.20 (ddq, J = 12.0, 7.7, 4.6 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.21 (ddd, J = 13.4, 7.4, 3.8 Hz, 1H), 3.09 (d, J = 12.3 Hz, 2H), 2.83 (h, J = 6.9, 6.3 Hz, 2H), 2.70 – 2.63 (m, 2H), 2.06 (dddt, J = 17.4, 13.0, 8.2, 5.1 Hz, 4H), 1.94 (d, J = 12.5 Hz, 2H), 1.73 (dt, J = 13.7, 6.3 Hz, 5H), 1.45 (d, J = 6.9 Hz, 3H), 1.37 – 1.26 (m, 2H), 1.14 – 1.09 (m, 2H), 1.00 – 0.96 (m, 2H). LCMS analysis (METCR1673 Generic 2 minutes), 94%, 0.90 min, $[MH]^{+}$=411.00.

Step 5: Chiral separation of 5-cyclopropyl-N-[2-methyl-1-(piperidin-4-ylmethanesulfonyl)piperidin-4-yl]-1,2-oxazole-3-carboxamide



Cpd. No. 417



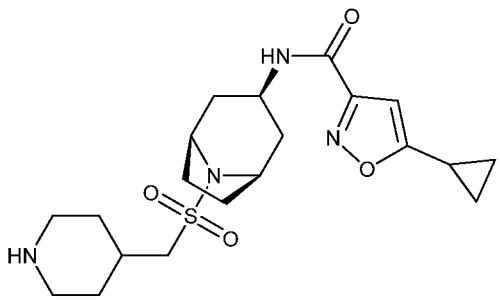
Cpd. No. 418

[0337] The racemic mixture of 5-cyclopropyl-N-(2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (94%, 636 mg, 1.46 mmol) of the cis isomers were purified by chiral separation using the following conditions: 25% Methanol + 0.1% DEA: 80% CO2 with Chiralpak AD-H 25cm column at 15ml/min. 254

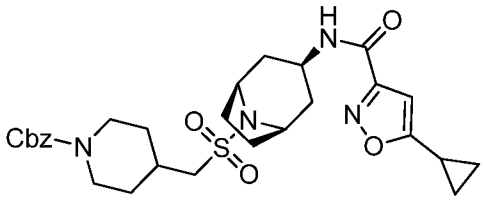
mg (43%) of racemic mixture was recovered. 118 mg (20%) of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (arbitrarily assigned as (S,S)-isomer) was isolated at 100% ee, having a retention time on chiral column of 3.21 min. ^{1}H NMR (500 MHz, Methanol-d4) δ 6.36 (s, 1H), 4.10 (tt, J = 9.1, 4.6 Hz, 1H), 3.77 (ddd, J = 13.4, 6.7, 4.0 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.15 (ddd, J = 13.2, 8.5, 3.7 Hz, 1H), 3.07 – 3.02 (m, 2H), 3.01 – 2.93 (m, 2H), 2.63 (td, J = 12.5, 2.7 Hz, 2H), 2.15 (tt, J = 8.5, 5.0 Hz, 1H), 2.12 – 1.90 (m, 5H), 1.77 – 1.67 (m, 2H), 1.41 (d, J = 6.7 Hz, 3H), 1.33 (qd, J = 12.0, 3.6 Hz, 2H), 1.16 – 1.10 (m, 2H), 0.98 – 0.94 (m, 2H). LCMS analysis (METCR1416 Hi res 7 min), 100%, 2.74 min, $[MH]^{+\cdot}$=411.00. 119 mg (19%) of 5-cyclopropyl-N-((2R,4R)-2-methyl-1-((piperidin-4-ylmethyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (arbitrarily assigned as (R,R) isomer) was isolated at 96% ee, having a retention time on chiral column of 4.77 min. ^{1}H NMR (500 MHz, Methanol-d4) δ 6.36 (s, 1H), 4.10 (tt, J = 9.1, 4.6 Hz, 1H), 3.77 (ddd, J = 13.4, 6.7, 4.0 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.15 (ddd, J = 13.0, 8.5, 3.7 Hz, 1H), 3.04 (d, J = 12.7 Hz, 2H), 3.02 – 2.93 (m, 2H), 2.64 (td, J = 12.5, 2.6 Hz, 2H), 2.15 (tt, J = 8.4, 5.0 Hz, 1H), 2.12 – 1.91 (m, 5H), 1.77 – 1.67 (m, 2H), 1.41 (d, J = 6.7 Hz, 3H), 1.33 (qd, J = 12.0, 3.1 Hz, 2H), 1.15 – 1.11 (m, 2H), 0.98 – 0.94 (m, 2H). LCMS analysis (METCR1416 Hi res 7 min), 100%, 2.74 min, $[MH]^{+\cdot}$=410.95.

EXAMPLE 18

Synthesis of 5-cyclopropyl-N-((1R, 3r, 5S)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo [3.2.1] octan-3-yl) isoxazole-3-carboxamide (Cpd. No. 543)

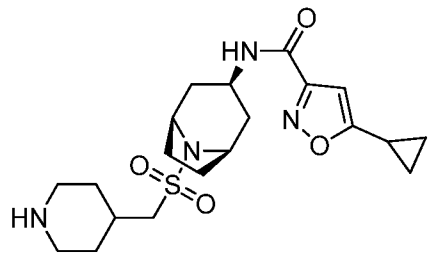


Step 1: Synthesis of benzyl 4-(((1S,3r,5R)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



[0338] Into a 25-mL round-bottom flask was placed N-((1S,3R,5R)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (80 mg, 0.27 mmol, 1.00 equiv), dichloromethane (5 mL), TEA (81 mg, 0.80 mmol, 3.00 equiv), and 4-dimethylaminopyridine (33 mg, 0.27 mmol, 1.00 equiv). This was followed by the addition of benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (140 mg, 0.42 mmol, 1.50 equiv) dropwise at 0°C. The resulting solution was stirred for 4 h at 25°C. The reaction was quenched with water/ice (20 mL) and extracted with EA (20mL, three times). The organic extracts were combined and washed with brine (20mL), then dried over with Na_2SO_4. After evaporation, the residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (2:3). This resulted in 70 mg (47%) of benzyl 4-(((1S, 3R, 5R)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo [3.2.1] octan-8-ylsulfonyl) methyl) piperidine-1-carboxylate as a yellow solid. LCMS (method A, ESI): RT = 1.09 min, m/z = 557.0 $[M+H]^+$.

Step 2: Synthesis of 5-cyclopropyl-N-((1R, 3rR, 5S)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo [3.2.1] octan-3-yl) isoxazole-3-carboxamide

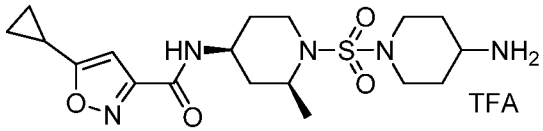


[0339] Into a 25-mL round-bottom flask was placed benzyl 4-(((1S, R, 5R)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo [3.2.1] octan-8-ylsulfonyl) methyl) piperidine-1-carboxylate (70 mg, 0.13 mmol, 1.00 equiv) and hydrochloric acid (12N, 3mL). The resulting solution was stirred for 2 h at 25°C. The residue was concentrated under vacuum. The crude product (32.9 mg) was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, silica gel; mobile phase: (phase A: 0.5% NH_4HCO_3 in H_2O, phase B: CH_3CN) B/A=5% increasing to B/A=80% within 15 min; Detector, UV 254 nm. This resulted in 14.4 mg (27%) of 5-cyclopropyl-N-((1S, 3R, 5R)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo [3.2.1] octan-3-yl) isoxazole-3-

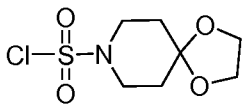
carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ6.48(s, 1H), 4.56(s, 2H), 4.20-4.16(m, 1H), 3.34-3.02(m, 4H), 2.66-2.59(m, 2H), 2.31-1.92(m, 12H), 1.34-1.30(m, 2H), 1.18-1.13(m, 2H), 1.01-0.97(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.36 min, m/z = 423.3 $[M+H]^+$.

EXAMPLE 19

Synthesis of N-((2S,4S)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide trifluoroacetic acid (Cpd. No. 529)

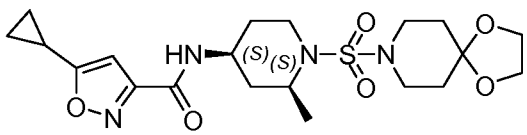


Step 1: Synthesis of 1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl chloride



[0340] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed dichloromethane (30 mL) and sulfuryl chloride (5.1 g, 37.79 mmol, 1.08 equiv). This was followed by the addition of a solution of 1,4-dioxa-8-azaspiro[4.5]decane (5 g, 34.92 mmol, 1.00 equiv) and 4-dimethylaminopyridine (4.27 g, 34.95 mmol, 1.00 equiv) in dichloromethane (10 mL) dropwise with stirring at -78°C. The resulting solution was stirred for 4 hours at 25°C. The resulting mixture was concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/ petroleum ether (1:10). This resulted in 4.2 g (50%) of 1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl chloride as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.02(s, 4H), 3.51(s, 4H), 1.94-1.91(m, 4H) *ppm*.

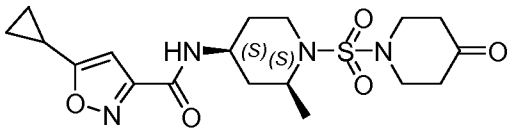
Step 2: Synthesis of 5-cyclopropyl-N-[(2S,4S)-1-[1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl]-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide



[0341] Into a 50-mL round-bottom flask was placed dichloromethane (15 mL), triethylamine (500 mg, 4.94 mmol, 4.71 equiv), and 5-cyclopropyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride (300 mg, 1.05 mmol,

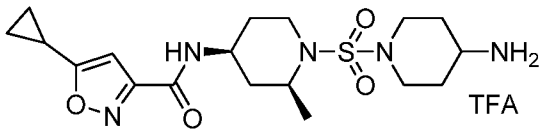
1.00 equiv). This was followed by the addition of a solution of 1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl chloride (700 mg, 2.90 mmol, 2.76 equiv) in dichloromethane (5 mL) dropwise with stirring at -78°C. The resulting solution was stirred for 16 hours at 25°C. The reaction mixture was washed with brine (sat. aq., 3 x 10 mL) and the organic layerconcentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (3:7). This resulted in 300 mg (63%) of 5-cyclopropyl-N-[(2S,4S)-1-[1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl]-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.82(d, *J*=7.2 Hz, 1H), 6.34(s, 1H), 4.24-4.22(m, 1H), 3.98(s, 4H), 3.73-3.70(m, 1H), 3.63-3.60(m, 1H), 3.35-3.27(m, 5H), 2.11-2.00(m, 3H), 1.80-1.73(m, 6H), 1.45(d, *J*=6.8Hz, 3H), 1.16-1.12(m, 2H), 1.02-0.98(m, 2H) *ppm*. LCMS (method D, ESI): RT =1.91 min, *m/z* = 455.5 $[M+H]^+$.

Step 3: Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-(4-oxopiperidin-1-ylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide



[0342] Into a 25-mL round-bottom flask was placed THF (10 mL), 5-cyclopropyl-N-[(2S,4S)-1-[1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonyl]-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide (300 mg, 0.66 mmol, 1.00 equiv) and hydrochloric acid (2N, 5 mL). The resulting solution was stirred for 16 hour at 25°C. The pH value of the solution was adjusted to 8 with Na_2CO_3 (sat. aq.). The resulting mixture was concentrated under vacuum. The resulting mixture was diluted with 10 mL of DCM. The solids were filtered off yielding250 mg (92%) of 5-cyclopropyl-N-[(2S,4S)-2-methyl-1-(4-oxopiperidine-1-sulfonyl)piperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.83 (d, *J*=6.38Hz, 1H), 6.34(s, 1H), 4.26-4.24(m, 1H), 3.72-3.66(m, 2H), 3.59-3.56(m, 4H), 3.34-3.32(m, 1H), 2.60-2.56(m, 4H), 2.11-2.04(m, 3H), 1.82-1.76(m, 2H), 1.48 (d, *J*=6.8Hz, 3H), 1.15-1.12(m, 2H), 1.02-1.00(m, 2H) *ppm*. LCMS (method D, ESI): RT =1.32 min, *m/z* = 411.2 $[M+H]^+$.

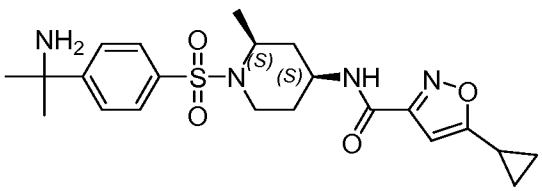
Step 4: Synthesis of N-((2S,4S)-1-(4-aminopiperidin-1-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide trifluoroacetic acid



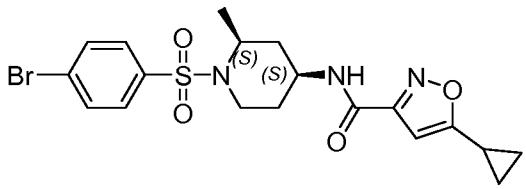
[0343] Into a 250-mL round-bottom flask was placed methanol (100 mL), 5-cyclopropyl-N-[(2S,4S)-2-methyl-1-(4-oxopiperidine-1-sulfonyl)piperidin-4-yl]-1,2-oxazole-3-carboxamide (60 mg, 0.15 mmol, 1.00 equiv), and ammonium formate (500 mg, 7.93 mmol, 54.25 equiv). Then $NaBH_3CN$ (30 mg, 0.48 mmol, 3.27 equiv) was added at 0°C. The resulting solution was stirred for 16 hours at 25°C. The reaction mixture was concentrated under vacuum and the residuediluted with 20 mL of dichloromethane. The resulting mixture was washed with brine (sat. aq., 2 x 10 mL). The organic layer was concentrated under vacuum and the crude product purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-005(Waters)): Column, Atlantis Prep OBD T3 Column,19*150mm,5um,; mobile phase, water with 0.05% TFA and CH_3CN (up to 3.0% in 10 min, up to 100.0% in 1 min, hold 100.0% in 1 min); Detector, UV 254 nm. This resulted in 26.4 mg (34%) of N-[(2S,4S)-1-(4-aminopiperidine-1-sulfonyl)-2-methylpiperidin-4-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide trifluoroacetate as a white solid. ^1H NMR (400 MHz, CD_3OD) δ : 6.38(s, 1H), 4.13-4.05(m, 1H), 3.80-3.77(m, 3H), 3.76-3.74(m, 1H), 3.33-3.23(m, 2H), 2.93(t, *J*=12.4Hz, 2H), 2.19-2.15(m, 1H), 2.07-1.95(m, 4H), 1.82-1.67(m, 4H), 1.42 (d, *J*=6.8Hz, 3H), 1.18-1.13(m, 2H), 1.00-0.97(m, 2H) *ppm*. LCMS (method A, ESI): RT =1.71 min, *m/z* = 412.5 $[M-TFA+H]^+$.

EXAMPLE 20

Synthesis of N-((2S,4S)-1-(4-(2-aminopropan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 541)

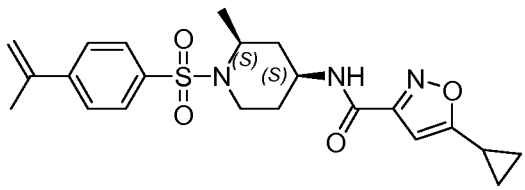


Step 1: Synthesis of N-((2S,4S)-1-(4-bromophenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0344] Into a 100-mL round-bottom flask was placed 5-cyclopropyl-N-[(2S,4S)-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide hydrochloride (1 g, 3.50 mmol, 1.00 equiv) and dichloromethane (10 mL). This was followed by the dropwise addition of TEA (1.1 g, 10.87 mmol, 3.11 equiv) with stirring at 0°C. To this was added 4-bromobenzene-1-sulfonyl chloride (900 mg, 3.52 mmol, 1.01 equiv) in several batches at 0°C. The resulting solution was stirred at room temperature for overnight. The reaction mixture was diluted with 10 mL of H_2O andextracted with 3x20 mL of dichloromethane. Theorganic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:10-1:2). This resulted in 1.6 g (98%) of N-((2S,4S)-1-(4-bromophenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75-7.64 (m, 4H), 6.75 (d, *J* =6.4 Hz, 1H), 6.32 (s, 1H), 4.17-4.03 (m, 1H), 3.80-3.69 (m, 1H), 3.67-3.53 (m, 1H), 3.30-3.18 (m, 1H), 2.12-2.03 (m, 1H), 2.03-1.92 (m, 2H), 1.82-1.66 (m, 2H), 1.33 (d, *J* =6.8 Hz, 3H), 1.19-1.09 (m, 2H), 1.03-0.95 (m, 2H) *ppm*. LCMS (Method A, ESI): RT=1.54 min, *m/z* =468.0 $[M+H]^+$.

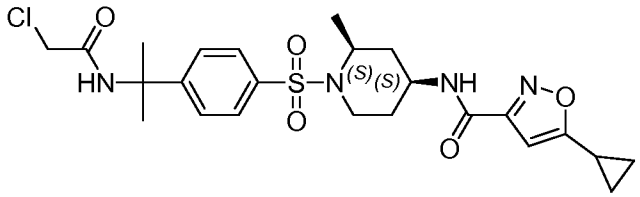
Step 2: Synthesis of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-(4-(prop-1-en-2-yl)phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide



[0345] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed N-((2S,4S)-1-(4-bromophenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (1 g, 2.14 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ (160 mg, 0.22 mmol, 0.10 equiv), K_2CO_3 (880 mg, 6.32 mmol, 2.96 equiv), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (540 mg, 3.21 mmol, 1.51 equiv), 1,4-dioxane (10 mL) and water(1 mL). The resulting solution was stirred at 90°C overnight. The reaction mixture was diluted with 10 mL of H_2O andextracted with 3x50 mL of ethyl acetate. Theorganic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:10-1:2). This resulted in 480 mg (52%) of 5-cyclopropyl-N-((2S,4S)-2-methyl-1-(4-(prop-1-en-2-yl)phenylsulfonyl)piperidin-4-

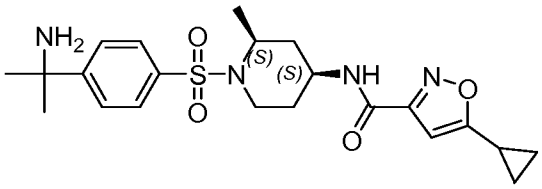
yl)isoxazole-3-carboxamide as a light yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* =8.7 Hz, 2H), 7.58 (d, *J* =8.7 Hz, 2H), 6.73 (d, *J* =6.6 Hz, 1H), 6.30 (s, 1H), 5.48 (s, 1H), 5.24 (s, 1H), 4.17-3.98 (m, 1H), 3.81-3.68 (m, 1H), 3.61-3.47 (m, 1H), 3.28-3.12 (m, 1H), 2.18 (s, 3H), 2.11-1.92 (m, 3H), 1.79-1.60 (m, 2H), 1.33 (d, *J* =6.6 Hz, 3H), 1.16-1.05 (m, 2H), 1.02-0.91 (m, 2H) *ppm*. LCMS (Method D, ESI): RT=1.61 min, *m/z* =430.0 $[M+H]^+$.

Step 3: Synthesis of N-((2S,4S)-1-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0346] Into a 100-mL round-bottom flask was placed 5-cyclopropyl-N-((2S,4S)-2-methyl-1-(4-(prop-1-en-2-yl)phenylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide (480 mg, 1.12 mmol, 1.00 equiv), 2-chloroacetonitrile (1.67 g, 22.12 mmol, 19.79 equiv), and acetic acid (28 mL). After cooling to 0°C sulfuric acid (98%, 7 mL) was added dropwise. The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with of ice-water and the pH of the solution was adjusted to 7 with sodium carbonate (sat. aq.). The resulting solution was extracted with 3x50 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate. The residue was chromatographed on a silica gel column with dichloromethane/methanol (20:1). This resulted in 580 mg (99%) of N-((2S,4S)-1-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 7.78 (d, *J* =8.7 Hz, 2H), 7.62 (d, *J* =8.7 Hz, 2H), 6.34 (s, 1H), 4.09-3.99 (m, 3H), 3.95-3.80 (m, 2H), 3.17-3.00 (m, 1H), 2.20-2.08 (m, 1H), 2.03-1.79 (m, 2H), 1.77-1.56 (m, 8H), 1.33 (d, *J* =6.6 Hz, 3H), 1.19-1.09 (m, 2H), 1.00-0.91 (m, 2H) *ppm*. LCMS (Method D, ESI): RT=0.97 min, *m/z* =523.0 $[M+H]^+$.

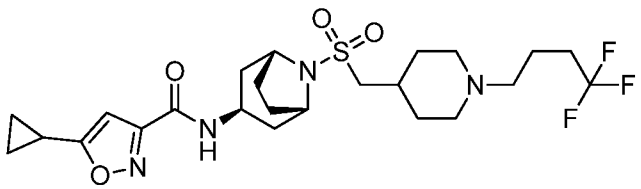
Step 4: Synthesis of N-((2S,4S)-1-(4-(2-aminopropan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide



[0347] Into a 25-mL round-bottom flask was placed N-((2S,4S)-1-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (150 mg, 0.29 mmol, 1.00 equiv), acetic acid (0.3 mL), ethanol (1.5 mL) and thiourea (26 mg, 0.34 mmol, 1.19 equiv). The resulting solution was stirred at 85°C overnight. The reaction mixture was concentrated under vacuum and the residue diluted with 10 mL of H_2O. The resulting solution was extracted with 3x5 mL of ethyl acetate and the organic layers combined. The combined extracts were concentrated under vacuum and the crude product (98 mg) was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: Water/10mmol/L NH_4HCO_3, Mobile Phase B: MeOH; Flow rate: 30 mL/min; Gradient: 45%B to 75%B in 06 min; 254nm. 100 mL product was obtained. This resulted in 24 mg (19%) of N-((2S,4S)-1-(4-(2-aminopropan-2-yl)phenylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.85-7.71 (m, 4H), 6.35 (s, 1H), 3.92-3.80 (m, 2H), 3.41-3.33 (m, 1H), 3.16-3.07 (m, 1H), 2.21-2.10 (m, 1H), 2.00-1.91 (m, 1H), 1.91-1.82 (m, 1H), 1.76-1.62 (m, 2H), 1.54 (s, 6H), 1.34 (d, *J* =6.4 Hz, 3H), 1.19-1.09 (m, 2H), 1.00-0.91 (m, 2H) *ppm*. LCMS (Method B, ESI): RT=1.71 min, *m/z* =447.0 $[M+H]^+$.

EXAMPLE 21

Synthesis of 5-cyclopropyl-N-[(1R,3r,5S)-8-([[1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane]sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide (Cpd. No. 528)

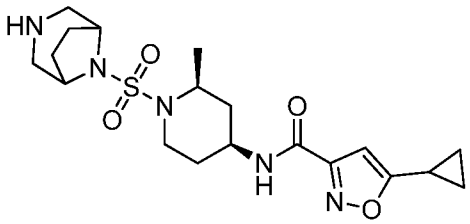


[0348] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-cyclopropyl-N-[(1R,3R,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide (68 mg,

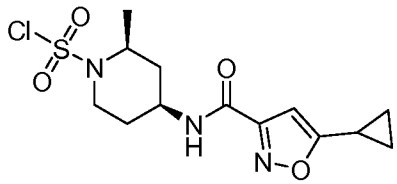
0.16 mmol, 1.00 equiv), methanol (2 mL), and 4,4,4-trifluorobutanal (41 mg, 0.33 mmol, 2.00 equiv). Then $NaBH_3CN$ (51 mg, 5.00 equiv) was added at 0°C. The resulting solution was stirred for 6 h at room temperature. The reacton mixture was concentrated under vacuum. The residue was dissolved in DCM (10 mL) and washed with saturated brine (10 mL). The organic phase was collected and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Prep-HPLC-019): Column, XBridge Prep C18 OBD Column, 19*100mm 5um 13nm; mobile phase, Water with 10mmolNH_4HCO_3 and MeCN (30.0% MeCN up to 60.0% in 6 min); Detector, UV 254/220nm. This resulted in 23.6 mg (28%) of 5-cyclopropyl-N-[(1R,3R,5S)-8-([[1-(4,4,4-trifluorobutyl)piperidin-4-yl]methane]sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): 6.39(s, 1H), 4.25(s, 2H), 4.17(t, *J* = 6.8 Hz, 1H), 3.07(d, *J* = 5.6 Hz, 2H), 2.96(d, *J* = 11.6 Hz, 2H), 2.43(t, *J* = 7.6 Hz, 2H), 2.31-1.97(m, 16H), 1.81-1.74(m, 2H), 1.46(q, *J* = 12.4 Hz, 2H), 1.18-1.13(m, 2H), 1.00-0.95(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.52 min, m/z = 533.4 $[M+H]^+$.

EXAMPLE 22

Synthesis of N-((2S,4S)-1-(3,8-diaza-bicyclo[3.2.1]octan-8-ylsulfonyl)-2-methylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 555)



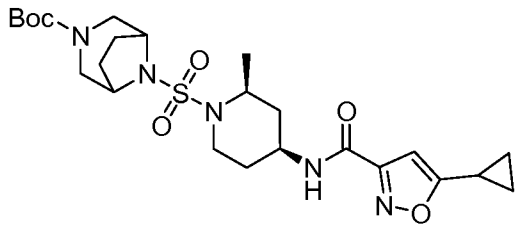
Step 1: Synthesis of (2S,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidine-1-sulfonyl chloride



[0349] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed solution of sulfuryl chloride (242 mg, 1.79 mmol, 1.50 equiv) in dichloromethane (10 mL) at -70°C. To this was added a solution of DIEA

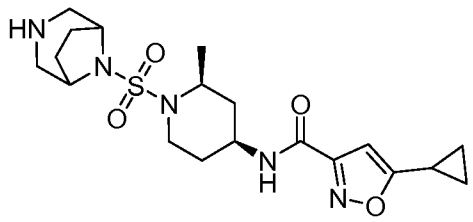
(621 mg, 4.81 mmol, 4.00 equiv) and 5-cyclopropyl-N-(3-methylpiperazin-1-yl)-1,2-oxazole-3-carboxamide (300 mg, 1.20 mmol, 1.00 equiv) in dichloromethane (5 mL) dropwise with stirring at -70°C. The resulting solution was stirred for 30 min at -70°C in a dry ice bath. The reaction mixture was concentrated under vacuum and theresidue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:4). The fractions containing product were combined and concentrated under vacuum. This resulted in 350 mg (84%) of 4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperazine-1-sulfonyl chloride as a white solid. LCMS (method D, ESI): RT = 0.98 min, m/z = 348 $[M+H]^+$.

Step 2: Synthesis of tert-butyl 8-((2S,4S)-4-(5-cyclopropylisoxazole-3-carboxamido)-2-methylpiperidin-1-ylsulfonyl)-3,8-diaza-bicyclo[3.2.1]octane-3-carboxylate



[0350] Into a 50-mL round-bottom flask was placed tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (366.6 mg, 1.73 mmol, 1.50 equiv), dichloromethane (20 mL), DIEA (298 mg, 2.31 mmol, 2.00 equiv), and 4-dimethylaminopyridine (14 mg, 0.11 mmol, 0.10 equiv). To this was added a solution of (2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-sulfonyl chloride (400 mg, 1.15 mmol, 1.00 equiv) in dichloromethane (2mL) dropwise with stirring at 0°C under nitrogen. The resulting solution was stirred overnight at room temperature. After concentration, the residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1/10-1/5). This resulted in 550 mg (91%) of tert-butyl 8-[(2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-sulfonyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate as colorless oil. LCMS (method D, ESI): RT = 1.26 min, m/z = 524.3 $[M+H]^+$.

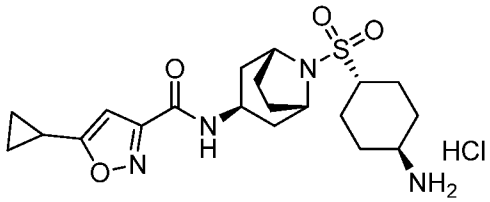
Step 3: Synthesis of 5-cyclopropyl-N-[(2S,4S)-1-[3,8-diazabicyclo[3.2.1]octane-8-sulfonyl]-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide



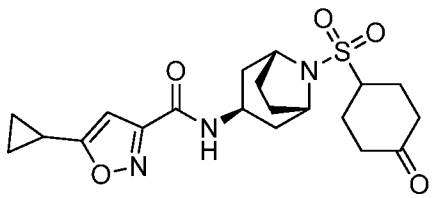
[0351] Into a 50-mL round-bottom flask was placed tert-butyl 8-[(2S,4S)-4-(5-cyclopropyl-1,2-oxazole-3-amido)-2-methylpiperidine-1-sulfonyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (550 mg, 1.05 mmol, 1.00 equiv), dichloromethane (20 mL) and trifluoroacetic acid (4 mL). The resulting solution was stirred for 2.5 h at room temperature. The reaction mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, Sunfire C18 19*150, mobile phase, CH_3CN:NH_4CO_3/H_2O (10mmol/L) = 20%-55%, 20min, Detector UV 254nm. This resulted in 355.4 mg (80%) of 5-cyclopropyl-N-[(2S,4S)-1-[3,8-diazabicyclo[3.2.1]octane-8-sulfonyl]-2-methylpiperidin-4-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.90-6.71 (m, 1H), 6.32 (s, 1H), 4.28-4.15(m, 1H), 3.78-3.68(m, 1H), 3.67-3.50(m, 3H), 3.4 -3.28(m, 2H), 3.27-3.15 (m, 1H), 3.10-3.00(m, 2H), 2.20-2.00(m, 4H), 1.89-1.69(m, 6H), 1.50-1.39(m, 3H), 1.20-1.06(m, 2H) , 1.05-0.90(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.73 min, m/z = 424.0 $[M+H]^+$.

EXAMPLE 23

Synthesis of N-((1R,3R,5S)-8-((1r,4R)-4-aminocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (Cpd. No. 539)

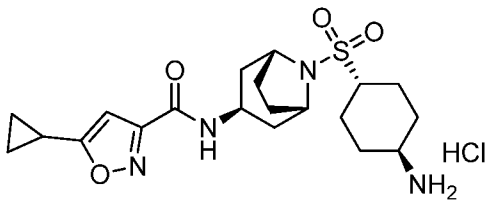


Step 1: Synthesis of 5-cyclopropyl-N-((1R,3r,5S)-8-(4-oxocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide



[0352] Into a 2-L 3-necked round-bottom flask was placed a solution of N-((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (20 g, 67.16 mmol, 1.00 equiv) in dichloromethane (800 mL). Then DIEA (43 g, 332.71 mmol, 5.00 equiv) was added, followed by the addition of 4-oxocyclohexane-1-sulfonyl chloride (14.45 g, 73.48 mmol, 1.10 equiv) in portions over 5.5 hr (0.1 equiv for each portion). The resulting solution was stirred overnight at 20°C. The reaction mixture was washed with dilute hydrochloric acid (1N, 200 mL). Then the organic phase was washed with $NaHCO_3$ (sat. 200 mL) and brine (sat. 200 mL) respectively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. This resulted in 19 g (64%) of 5-cyclopropyl-*N*-((1R,3r,5S)-8-(4-oxocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.14(d, *J* = 9 Hz, 1H), 6.34(s, 1H), 4.37-4.25(m, 3H), 3.36-3.27(m, 1H), 2.65-2.15(m, 10H), 2.13-1.9(m, 7H), 1.20-1.10(m, 2H), 1.05-0.95(m, 2H) *ppm*. LCMS (method C, ESI): RT = 0.88 min, *m/z* = 422.2 $[M+H]^+$.

Step 2: Synthesis of N-((1R,3R,5S)-8-(((1r,4R)-4-aminocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride

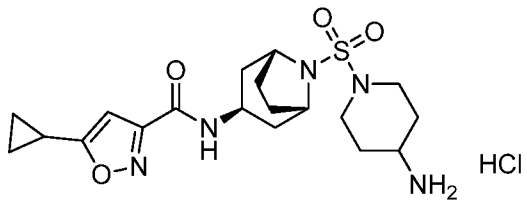


[0353] Into a 5-L round-bottom flask was placed a solution of 5-cyclopropyl-*N*-((1R,3r,5S)-8-(4-oxocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (3 g, 7.12 mmol, 1.00 equiv) in methanol (3 L), then $HCOONH_4$ (17.6 g, 279.12 mmol, 40.00 equiv) and acetic acid (852 mg, 14.19 mmol, 2.00 equiv) were added. After stirred for 30 min at 25°C, $NaBH_3CN$ (895 mg, 14.24 mmol, 2.00 equiv) was added portion-wise. The resulting solution was stirred for 30 min at 25°C. The reaction mixture was concentrated under vacuum. The resulting solid was extracted with ethyl acetate (100 mLx5). The combined organic extracts were concentrated and the residue purified by flash chromatography (DCE: MeOH = 10:1). The crude product was further purified by Prep-HPLC with the following conditions: Column, X Bridge C18, 19*150 mm, 5 um; mobile phase, Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Detector, 254 nm. The fractions containing product were combined and concentrated. They were then treated with hydrochloric acid (12N, 1 mL)

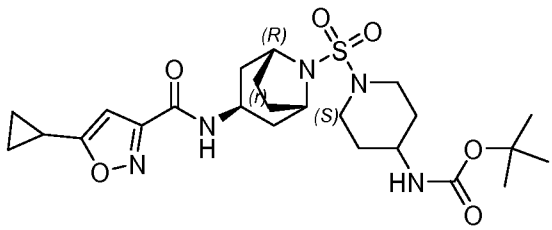
and concentrated again under vacuum. This resulted in 1.0 g (31%) of N-((1R,3R,5S)-8-((*1r,4R*)-4-aminocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride as a light yellow solid. ^{1}H-NMR (300 MHz, D_2O): δ 6.29(s, 1H), 4.21-4.00(m, 3H), 3.28-3.10(m, 2H), 2.30-2.05(m, 7H), 2.05-1.87(m, 6H), 1.65-1.35(m, 4H), 1.12-1.00(m, 2H), 0.95-0.84(m, 2H) *ppm*. LCMS (method D, ESI): RT = 0.89 min, *m/z* =423.1 $[M+H]^+$.

EXAMPLE 24

Synthesis of N-((1R,3r,5S)-8-(4-aminopiperidin-1-ylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (Cpd. No. 532)



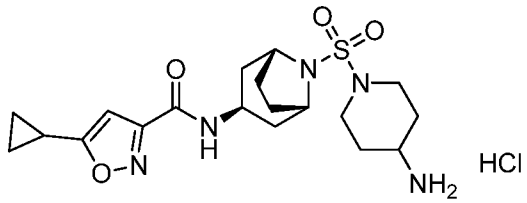
Step 1: Synthesis of tert-butyl 1-((1R,3r,5S)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)piperidin-4-ylcarbamate



[0354] Into a 250-mL round-bottom flask was placed tert-butyl N-(piperidin-4-yl)carbamate (1.2 g, 5.99 mmol, 4.00 equiv), dichloromethane (20 mL), and DIEA (2.2 g, 17.02 mmol, 10.00 equiv). After stirring for 30 min, (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl chloride (600 mg, 1.67 mmol, 1.00 equiv) was added at 0°C. The resulting solution was stirred for 12 h at 20°C. The reaction mixture was diluted by DCM (30 mL), and washed by water (10 mLx3). The organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with ethyl acetate/hexane (2:1). This resulted in 620 mg (71%) of tert-butyl 1-((1R,3r,5S)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)piperidin-4-ylcarbamate. ^{1}H-NMR (400 MHz,$CDCl_3$): δ 7.15(d, *J* = 7.2 Hz, 1H), 6.35(s, 1H), 4.50-

4.45(m, 1H), 4.36-4.28(m, 1H), 4.20-4.10(m, 2H), 3.75-3.50(m, 3H), 2.90-2.80(m, 2H), 2.35-2.22(m, 4H), 2.15-1.89(m, 7H), 1.55-1.43(m, 11H), 1.18-1.12(m, 2H), 1.04-0.96(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.45 min, m/z = 546.0 $[M+23]^+$.

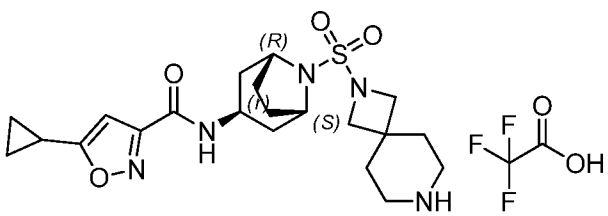
Step 2: Synthesis of N-((1R,3r,5S)-8-(4-aminopiperidin-1-ylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride



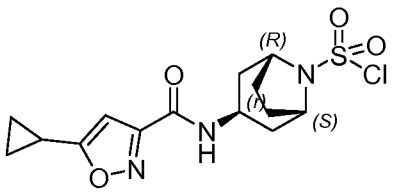
[0355] Into a 250-mL round-bottom flask was placed tert-butyl N-[1-[(1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]piperidin-4-yl]carbamate (600 mg, 1.15 mmol, 1.00 equiv) and dichloromethane (20 mL). Then hydrogen chloride (gas) was introduced into mixture. The resulting solution was stirred for 5 h at 20°C. The resulting mixture was concentrated under vacuum. The solids were collected by filtration. This resulted in 420 mg (87%) of N-((1R,3r,5S)-8-(4-aminopiperidin-1-ylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride as a white solid. ^{1}H-NMR (300 MHz,D_2O): δ 6.31(s, 1H), 4.09(s, 3H), 3.76(d, *J* = 9 Hz, 2H), 3.39-3.26(m, 1H), 2.97-2.84(m, 2H), 2.30-1.90(m, 11H), 1.74-1.56(m, 2H), 1.15-1.02(m, 2H), 0.96-0.86(m, 2H) *ppm*. LCMS (method B, ESI): RT=1.50 min, *m/z* =423.9 $[M+H]^+$.

EXAMPLE 25

Synthesis of N-((1R,3r,5S)-8-(2,7-diazaspiro[3.5]nonan-2-ylsulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide 2,2,2-trifluoroacetate (Cpd. No. 559)

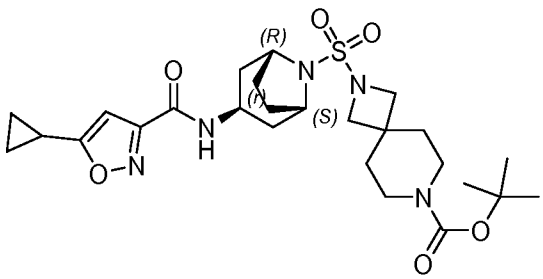


Step 1: Synthesis of (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl chloride



[0356] Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed sulfuryl chloride (451 mg, 3.34 mmol, 1.00 equiv). At -78°C, DIEA (870 mg, 6.73 mmol, 2.00 equiv) with N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-5-cyclopropyl-1,2-oxazole-3-carboxamide hydrochloride (1 g, 3.36 mmol, 1.00 equiv) in dichloromethane (50 mL) was added dropwise into the above solution at -78°C (in a liquid nitrogen bath) in 5 min. The resulting solution was allowed to warm to room temperature and stir overnight. The reaction mixture was concentrated under vacuum. The residue was dissolved in 40 ml of ethyl acetate. The resulting mixture was washed with 50 mL of diluted hydrochloric acid (1N). Then the mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 1 g (83%) of (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl chloride as a white solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 6.36(s, 1H), 4.45(s, 2H), 4.17(t, J = 12 Hz, 1H), 2.50-2.02(m, 9H), 1.17-1.09(m, 2H), 1.00-0.91(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.45 min, *m/z* =360.0 $[M+H]^+$.

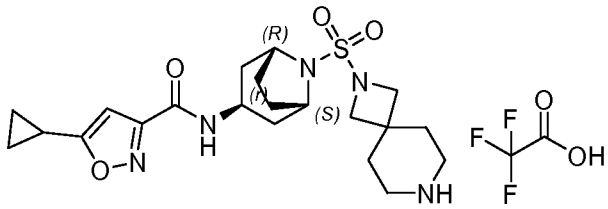
Step 2: Synthesis of tert-butyl 2-[(1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



[0357] Into a 50-mL round-bottom flask was placed tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate hydrochloride (876 mg, 3.33 mmol, 4.14 equiv), DIEA (1.07 mg, 0.01 mmol, 0.01 equiv), and dichloromethane (5 mL). After the mixture was stirred for 30 min, (1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl chloride (290 mg, 0.81 mmol, 1.00 equiv) was added. The resulting solution was stirred for 12 h at 20°C. The reaction mixture was diluted with 30 mL of dichloromethane and washed with water (10 mLx3). The organic phase was dried over anhydrous Na_2SO_4

and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with ethyl acetate/hexane (2:1). This resulted in 355 mg (75%) of tert-butyl 2-[(1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate as a white solid. ^{1}H-NMR (400 MHz,$CDCl_3$): δ 7.12(d, 1H), 6.32(s, 1H), 4.35-4.15(m, 3H), 3.60(s, 4H), 3.35(t, J = 12 Hz, 4H), 2.35-1.85(m, 9H), 1.74(t, J = 12 Hz, 4H), 1.45(s, 9H), 1.17-1.08(m, 2H), 1.03-0.96(m, 2H) *ppm*. LCMS (method B, ESI): RT = 1.52 min, m/z = 450.2 $[M-100]^+$.

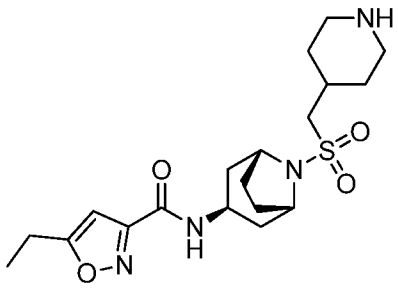
Step 3: Synthesis of 5-cyclopropyl-N-[(1R,3r,5S)-8-[2,7-diazaspiro[3.5]nonane-2-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide trifluoroacetate



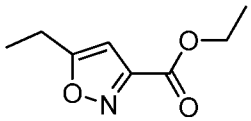
[0358] Into a 25-mL round-bottom flask was placed tert-butyl 2-[(1R,3r,5S)-3-(5-cyclopropyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (50 mg, 0.09 mmol, 1.00 equiv), dichloromethane (10 mL) and trifluoroacetic acid (2.5 mL). The resulting solution was stirred for 4 h at room temperature. The reaction mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 30%B to 70%B in 10 min; 254nm. This resulted in 36.5 mg (83%) of 5-cyclopropyl-N-[(1R,3r,5S)-8-[2,7-diazaspiro[3.5]nonane-2-sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide trifluoroacetate as a solid. ^{1}H-NMR (300 MHz, D_2O): δ 6.28(s, 1H), 4.08(s, 3H), 3.66(s, 4H), 3.15-3.05(m, 4H), 2.24-1.86(m, 13H), 1.08-099(m, 2H), 0.92-0.84(m, 2H) *ppm*. LCMS (method B, ESI): RT=1.67 min, *m/z* =450.0 $[M+H]^+$.

EXAMPLE 26

Synthesis of 5-ethyl-N-((1R,3r,5S)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (Cpd. No. 562)

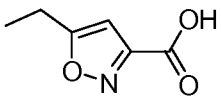


Step 1: Synthesis of ethyl 5-ethylisoxazole-3-carboxylate



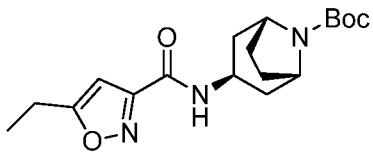
[0359] Into a 250-mL round-bottom flask was placed ethyl 2,4-dioxohexanoate (10 g, 69.36 mmol, 1.00 equiv), ethanol (100 mL), and NH_2OH-HCl (4.95 g, 70.23 mmol, 1.2 equiv). The resulting solution was stirred for 16 hours at 80°C in an oil bath. The reaction mixture was concentrated under vacuum and the residuedissolved in 50 mL of ethyl acetate. The resulting mixture was washed with 2x20 mL of water. The organic phase was dried and concentrated under vacuum. This resulted in 10 g (46%) of ethyl 5-ethyl-1,2-oxazole-3-carboxylate as a yellow solid. LCMS (method A, ESI): RT = 1.37 min, m/z =170.0 $[M+H]^+$.

Step 2: Synthesis of 5-ethylisoxazole-3-carboxylic acid



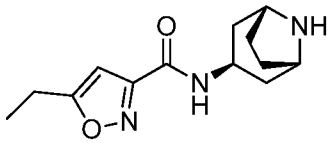
[0360] Into a 250-mL round-bottom flask was placed ethyl 5-ethyl-1,2-oxazole-3-carboxylate (5g, 29.55 mmol, 1.00 equiv), ethanol (50 mL), and sodium hydroxide (2.4 g, 60.00 mmol, 2.03 equiv). This was followed by the addition of water (8 mL) dropwise with stirring over 10 mins. The resulting solution was stirred for 16 hours at 25°C. The pH value of the solution was adjusted to 4 with hydrochloric acid (6N). The resulting solution was extracted with 50 mL of dichloromethane. The resulting mixture was concentrated under vacuum. This resulted in 3 g (72%) of 5-ethyl-1,2-oxazole-3-carboxylic acid as a yellow solid. ^{1}H-NMR (300MHz, DMSO): δ13.8(s, 1H), 6.58(s, 1H), 2.85(q, J_1= 7.5 Hz, 2H), 1.32(t, J= 7.5 Hz, 3H) *ppm*. LCMS (method C, ESI): RT = 2.60 min, m/z = 142.0411.0 $[M+H]^+$.

Step 3: Synthesis of (1R,3r,5S)-tert-butyl 3-(5-ethylisoxazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate



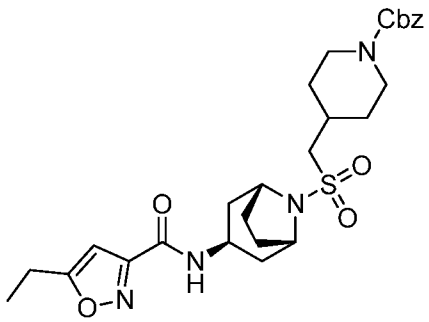
[0361] Into a 50-mL round-bottom flask was placed (1R,3r,5S)-tert-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (300 mg, 1.33 mmol, 1.00 equiv), dichloromethane (13 mL), 5-ethyl-1,2-oxazole-3-carboxylic acid (480 mg, 3.40 mmol, 1.10 equiv), 1-hydroxybenzotrizole (431 mg, 3.19 mmol, 1.50 equiv), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.2 g, 6.26 mmol, 3.00 equiv) and triethylamine (860 mg, 8.50 mmol, 4.00 equiv). The resulting solution was stirred for 16 h at 25°C. The reaction mixture was washed with 2x30 mL of H_2O. The water layers were back extracted with 2x30 mL of dichloromethane and the organic layers combined and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (6:1). This resulted in 350 mg (76%) of (1R,3r,5S)-tert-butyl 3-(5-ethylisoxazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylateas a yellow solid. LCMS (method C, ESI): RT = 0.93 min, m/z = 350.0 $[M+H]^+$.

Step 4: Synthesis of N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-ethylisoxazole-3-carboxamide



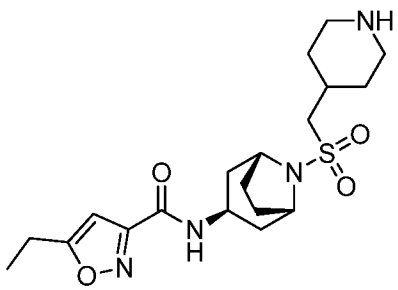
[0362] Into a 50-mL round-bottom flask was placed (1R,3r,5S)-tert-butyl 3-(5-ethylisoxazole-3-carboxamido)-8-azabicyclo[3.2.1]octane-8-carboxylate (350 mg, 1.00 mmol, 1.00 equiv) anddichloromethane (30 mL). To the above hydrogen chloride (gas) was introduced. The resulting solution was stirred for 2 h at 25°C. The reaction mixture was concentrated under vacuum. This resulted in 300 mg (HCl salt) of N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethyl-1,2-oxazole-3-carboxamide as a white solid. LCMS (method A, ESI): RT = 0.97 min, m/z = 250.0 $[M+H]^+$.

Step 5: Synthesis of benzyl 4-(((1R,3r,5S)-3-(5-ethylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



[0363] Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed N-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-5-ethyl-1,2-oxazole-3-carboxamide (100 mg, 0.40 mmol, 1.00 equiv), and tetrahydrofuran (5 mL). This was followed by the addition of lithium bis(trimethylsilyl)amide (1N in THF, 1.5 mL) dropwise with stirring at -70°C. To this was added benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (200 mg, 0.60 mmol, 1.50 equiv) in several portions at -70°C. The resulting solution was stirred for 30 min at -70°C in a dry ice bath. The reaction mixture was stirred for an additional 16 h at 25°C. The resulting solution was diluted with 30 mL of ethyl acetate andwashed with 2x15 mL of H_2O. The resulting mixture was concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (2:3). This resulted in 140 mg (64%) of benzyl 4-[[(1R,3r,5S)-3-(5-ethyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate as white solid. LCMS (method C, ESI): RT = 1.53 min, m/z = 545.0 $[M+H]^+$.

Step 6: Synthesis of 5-ethyl-N-((1R,3r,5S)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide

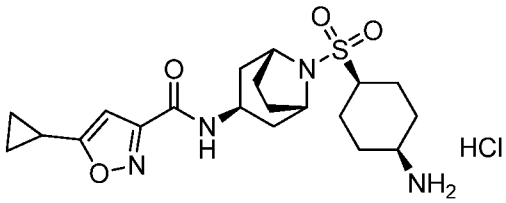


[0364] Into a 50-mL round-bottom flask was placed benzyl 4-[[(1R,3r,5S)-3-(5-ethyl-1,2-oxazole-3-amido)-8-azabicyclo[3.2.1]octane-8-sulfonyl]methyl]piperidine-1-carboxylate (120 mg, 0.22 mmol, 1.00 equiv) and hydrochloric acid (12N, 20 mL). The resulting solution was stirred for 2 h at 25°C. The reaction mixture was concentrated under vacuum. The crude product (120 mg) was purified by Prep-HPLC with the

following conditions (Prep-HPLC-025): Column, XBridge Prep Phenyl OBD Column,5um,19*150mm; mobile phase, Water with 10mmol NH_4HCO_3 and MeCN (20.0% MeCN up to 75.0% in 10 min, up to 95.0% in 1 min, hold 95.0% in 1 min, down to 20.0% in 2 min); Detector, UV 254/220nm.This resulted in 34.8 mg (38%) of 5-ethyl-N-[(1R,3r,5S)-8-[(piperidin-4-ylmethane)sulfonyl]-8-azabicyclo[3.2.1]octan-3-yl]-1,2-oxazole-3-carboxamide as a white solid. ^{1}H-NMR (400MHz, CD_3OD): δ 6.47(s, 1H), 4.26(d, *J*= 23.0 Hz, 2H), 4.16(d, *J*= 6.4 Hz, 1H), 3.14-3.06(m, 4H), 2.89(q, J_1=7.6Hz, J_2=15.2Hz, 2H), 2.76(q, J_1=10.8Hz, J_2= 12.8Hz, 2H), 2.32-2.26(m, 2H), 2.10-1.91(m, 9H), 1.44-1.38(m, 5H)*ppm*. LCMS (method C, ESI): RT = 2.60 min, m/z = 411.0 $[M+H]^+$.

EXAMPLE 27

Synthesis of N-((1R,3r,5S)-8-((1s,4S)-4-aminocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (Cpd. No. 540)

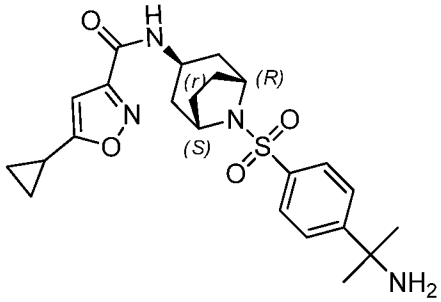


[0365] Into a 5-L round-bottom flask was placed a solution of 5-cyclopropyl-N-((1R,3r,5S)-8-((4-oxocyclohexyl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (3 g, 7.12 mmol, 1.00 equiv) in methanol (3 L). Then $HCOONH_4$ (17.6 g, 279.12 mmol, 40.00 equiv) and acetic acid (852 mg, 14.19 mmol, 2.00 equiv) were added. After stirring for 30 min at 25°C, $NaBH_3CN$ (895 mg, 14.24 mmol, 2.00 equiv) was added. The resulting solution was stirred for 30 min at 25°C. The reaction mixture was concentrated under vacuum. The resulting solid was extracted with ethyl acetate (100 mL X 5). The combined organic layers were concentrated and the residue purified by flash chromatography (DCE:MeOH = 10:1). The product was further purified by Prep-HPLC with the following conditions: Column, X Bridge C18, 19*150 mm, 5 um ; mobile phase, Mobile Phase A:Water/0.05% TFA, Mobile Phase B: ACN ; Flow rate: 20 mL/min; Detector, 254 nm. The fractions containing product were combined and concentrated, then acidified with hydrochloric acid (12N, 0.5mL), and concentrated again under vacuum. This resulted in 200 mg of N-((1R,3R,5S)-8-((1s,4S)-4-

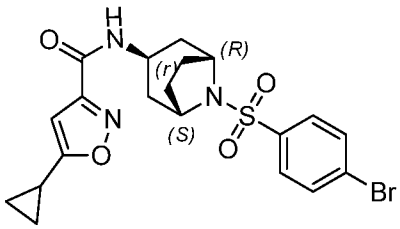
aminocyclohexylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride as a light yellow solid. ^{1}H-NMR (300 MHz, D_2O): δ 6.25(s, 1H), 4.15(s, 2H), 4.10-4.00(m, 1H), 3.42-3.25(m, 2H), 2.25-1.75(m, 17H), 1.09-1.00(m, 2H), 0.92-0.81(m, 2H) *ppm*. LCMS (method A, ESI): RT = 1.69 min, *m/z* = 445.2 $[M+23]^+$.

EXAMPLE 28

Synthesis of N-((1R,3r,5S)-8-(4-(2-aminopropan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide (Cpd. No. 766)



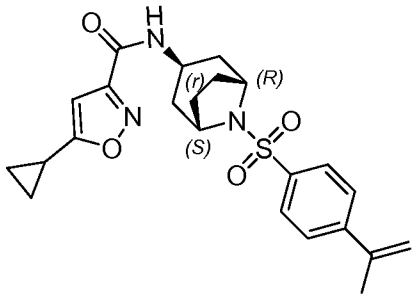
Step 1: Synthesis of N-((1R,3r,5S)-8-(4-bromophenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



[0366] Into a 25-mL round-bottom flask was placed N-((1R,3r,5S)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (500 mg, 1.68 mmol, 1.00 equiv), and dichloromethane (10 mL). This was followed by the dropwise addition of TEA (510 mg, 5.04 mmol, 3.00 equiv) with stirring at 0°C. To this was added 4-bromobenzene-1-sulfonyl chloride (470 mg, 1.84 mmol, 1.10 equiv) in several batches at 0°C. The resulting solution was stirred overnight at room temperature. The reaction mixture was diluted with 10 mL of dichloromethane. The resulting mixture was washed with 3x5 mL of H_2O. The organic phase was collected and concentrated under vacuum. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 742 mg (92%) of N-((1R,3r,5S)-8-(4-bromophenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-

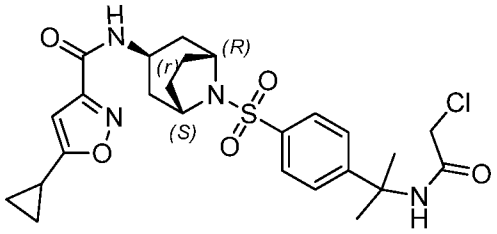
carboxamide as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78-7.70(m, 2H), 7.69-7.60(m, 2H), 7.04(br, 1H), 6.30(s, 1H), 4.28(brs, 3H), 2.39-2.25(m, 2H), 2.11-2.00(m, 1H), 1.97-1.72(m, 6H), 1.18-1.07(m, 2H), 1.00-0.92(m, 2H) *ppm*. LCMS (Method D, ESI): RT=1.57 min, *m/z* =480.0 $[M+H]^+$.

Step 2: Synthesis of 5-cyclopropyl-N-((1R,3r,5S)-8-(4-(prop-1-en-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide



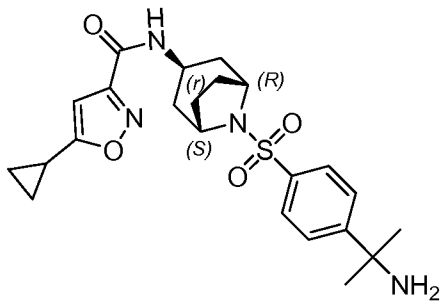
[0367] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed N-((1R,3r,5S)-8-(4-bromophenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide (642 mg, 1.34 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (293 mg, 1.74 mmol, 1.30 equiv), Pd(dppf)Cl_2 (98 mg, 0.13 mmol, 0.10 equiv), potassium carbonate (555 mg, 4.02 mmol, 3.00 equiv), 1,4-dioxane (15 mL) and water(1.5 mL). The resulting solution was stirred for 14 h at 90°C. The reaction mixture was concentrated under vacuum. The resulting solution was diluted with 25 mL of H_2O and extracted with 3x10 mL of ethyl acetate.The organic layers were combined and dried over anhydrous sodium sulfate. The residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 544 mg (92%) of 5-cyclopropyl-N-((1R,3r,5S)-8-(4-(prop-1-en-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.82(d, *J* =8.7 Hz, 2H), 7.56(d, *J* =8.7 Hz, 2H), 7.05(br, 1H), 6.30(s, 1H), 5.48(s, 1H), 5.24(s, 1H), 4.29(brs, 3H), 2.41-2.26(m, 2H), 2.17(s, 3H), 2.11-2.00(m, 1H), 1.97-1.70(m, 6H), 1.16-1.05(m, 2H), 1.01-0.92(m, 2H) *ppm*. LCMS (Method D, ESI): RT = 1.59 min, *m/z* = 442.0 $[M+H]^+$.

Step 3: Synthesis of N-((1R,3r,5S)-8-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide



[0368] Into a 100-mL round-bottom flask was placed 5-cyclopropyl-N-((1R,3r,5S)-8-(4-(prop-1-en-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (544 mg, 1.23 mmol, 1.00 equiv), AcOH (39 mL), 2-chloroacetonitrile (1.85 g, 24.50 mmol, 19.89 equiv). This was followed by the dropwise addition of sulfuric acid (98%, 9.7 mL) with stirring at 0°C. The resulting solution was stirred for 14 h at 25°C. The reaction mixture was diluted with 100 mL of ice-water. The pH of the solution was adjusted to 7 with sodium carbonate (sat. aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate. After concentration, the residue was chromatographed on a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 505 mg (77%) of N-((1R,3r,5S)-8-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.83(d, *J* =8.7 Hz, 2H), 7.48(d, *J* =8.4 Hz, 2H), 7.05(br, 1H), 6.85(brs, 1H), 6.30(s, 1H), 4.27(brs, 3H), 3.98(s, 2H), 2.40-2.26 (m, 2H), 2.11-2.00(m, 1H), 1.95-1.76(m, 6H), 1.75(s, 6H), 1.15-1.05(m, 2H), 1.00-0.91(m, 2H) *ppm*. LCMS (Method D, ESI): RT = 1.07 min, *m/z* = 535.0 $[M+H]^+$.

Step 4: Synthesis of N-((1R,3r,5S)-8-(4-(2-aminopropan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide

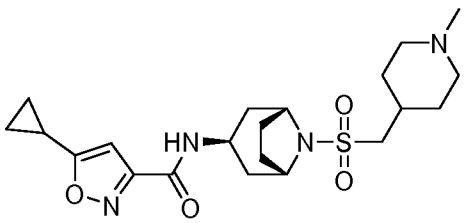


[0369] Into a 25-mL round-bottom flask was placed N-((1R,3r,5S)-8-(4-(2-(2-chloroacetamido)propan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide (593 mg, 1.11 mmol, 1.00 equiv), ethanol (6.0 mL), and thiourea (101 mg, 1.33 mmol, 1.20 equiv). This was followed by the dropwise

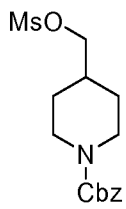
addition of AcOH (1.2 mL) with stirring. The resulting solution was stirred for 12 h at 85°C. The reaction mixture was concentrated under vacuum. The residue was dissolved in 10 mL of ethyl acetate and washed with 2x5 mL of H_2O. Concentraton yielded 465 mg (91%) of N-((1S,3r,5R)-8-(4-(2-aminopropan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide as an off-white solid. The crude product (100 mg) was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 um; Mobile Phase A: Water/10mmol/L NH_4HCO_3, Mobile Phase B: MeOH; Flow rate: 30 mL/min; Gradient: 45%B to 75%B in 06 min; 254nm. 120 mL of fractions contained product was obtainedresulting in 18.4 mg of N-((1R,3r,5S)-8-(4-(2-aminopropan-2-yl)phenylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.87(d, *J* =8.8 Hz, 2H), 7.73(d, *J* =8.4 Hz, 2H), 6.35(s, 1H), 4.27(brs, 2H), 4.20-4.10(m, 1H), 2.32-2.21(m, 2H), 2.20-2.10(m, 1H), 2.00(d, *J* =14.4Hz, 2H), 1.93-1.82(m, 2H), 1.63-1.55(m, 2H), 1.54(s, 6H), 1.18-1.10(m, 2H), 1.00-0.91(m, 2H) *ppm*. LCMS (Method A, ESI): RT=1.77 min, *m/z* = 481.0 $[M+Na]^+$.

EXAMPLE 29

Synthesis of 5-cyclopropyl-N-((1*S*,3*r*,5*R*)-8-((1-methylpiperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide (Cpd. No. 770)



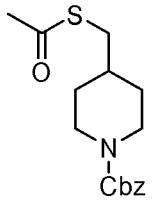
Step 1: Synthesis of benzyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate



[0370] Into a 1000-mL round-bottom flask, was placed benzyl 4-(hydroxymethyl)piperidine-1-carboxylate (100 g, 401.11 mmol, 1.00 equiv), dichloromethane (300 mL), triethylamine (121 g, 1.20 mol, 3.00 equiv). This was

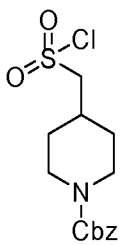
followed by the addition of methanesulfonyl chloride (91.6 g, 799.64 mmol, 2.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 16 h at 25°C. The resulting mixture was washed with 2x500 mL of H_2O. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 116 g (88%) of benzyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40-7.29(m, 5H), 5.07(s, 2H), 4.08-4.01(m, 4H), 3.17(s, 3H), 2.90-2.70(m, 2H), 1.99-1.86(m, 1H), 1.69-1.66(m, 2H), 1.20-1.15(m, 2H)*ppm*. LCMS (method D, ESI): RT=1.46 min, m/z=328.0 $[M+H]^+$.

Step 2: Synthesis of benzyl 4-(acetylthiomethyl)piperidine-1-carboxylate



[0371] Into a 2000-mL round-bottom flask, was placed benzyl 4-[(methanesulfonyloxy)methyl]piperidine-1-carboxylate (116 g, 354.31 mmol, 1.00 equiv), acetonitrile (1000 mL), 1-(potassiosulfanyl)ethan-1-one (190 g, 1.66 mol, 5.00 equiv). The resulting solution was stirred for 2 h at 80°C in an oil bath. The resulting solution was extracted with 2x500 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 105 g (96%) of benzyl 4-(acetylthiomethyl)piperidine-1-carboxylate as red oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40-7.29(m, 5H), 5.12(s, 2H), 4.20-4.13(m, 2H), 2.83-2.70(m, 4H), 2.34(s, 3H), 1.78-1.70(m, 2H), 1.68-1.57(m, 1H), 1.28-1.22(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.53 min, m/z=308.0 $[M+H]^+$

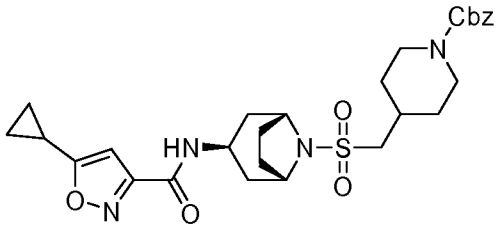
Step 3: Synthesis of benzyl 4-(chlorosulfonylmethyl)piperidine-1-carboxylate



[0372] Into a 1000-mL round-bottom flask, was placed benzyl 4-[(acetylsulfanyl)methyl]piperidine-1-carboxylate (105 g, 341.57 mmol, 1.00 equiv), acetic acid (500 mL), water(250 mL). This was followed by the addition of N-

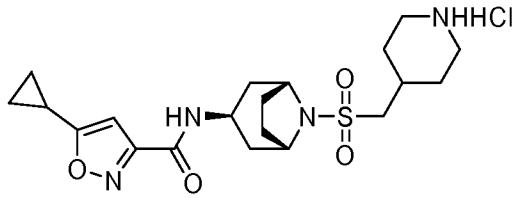
chlorosuccinimide (160 g, 1.20 mol, 3.50 equiv) in several batches at 0°C. The resulting solution was stirred for 2 h at 25°C. The resulting solution was extracted with 2x500 mL of dichloromethane and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4). This resulted in 95 g (84%) of benzyl 4-(chlorosulfonylmethyl)piperidine-1-carboxylate as a light yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41-7.28(m, 5H), 5.12(s, 2H), 4.24-4.08 (m, 2H), 3.65(d, *J*=6.3 Hz, 2H), 2.89-2.73(m, 3H), 2.43-2.31(m, 1H), 2.07-1.95(m, 2H), 1.43-1.21(m, 2H) *ppm*. LCMS (method A, ESI): RT=1.48 min, m/z=332.0 $[M+H]^+$.

Step 4: Synthesis of benzyl 4-(((1*S*,3*r*,5*R*)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate



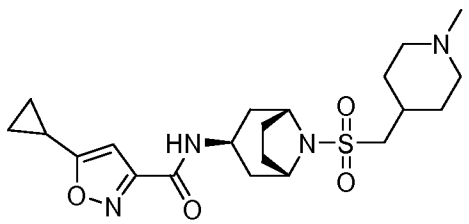
[0373] Into a 1000-mL round-bottom flask, was placed N-((1S,3r,5R)-8-aza-bicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide hydrochloride (28.4 g, 95.37 mmol, 1.00 equiv), dichloromethane (500 mL), triethylamine (100 g, 988.24 mmol, 10.00 equiv). This was followed by the addition of benzyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (35 g, 105.48 mmol, 1.10 equiv) in several batches at -70°C. The resulting solution was stirred for 16 h at 25°C. The resulting mixture was washed with 2x300 mL of H_2O. The organic phase was collected. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 34 g (64%) of benzyl 4-(((1S,3r,5R)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36-7.26(m, 5H), 7.10(d, *J*=7.2 Hz, 1H), 6.32(s, 1H), 5.12(s, 2H), 4.31-4.16(m, 5H), 2.92-2.84(m, 4H), 2.31-1.92(m, 12H), 1.31-1.24(m, 2H), 1.14-1.09(m, 2H), 1.01-0.97(m, 2H) *ppm*. LCMS (method B, ESI): RT=1.59 min, m/z=557.0$[M+H]^+$.

Step 5: Synthesis of 5-cyclopropyl-N-((1*S*,3*r*,5*R*)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide hydrochloride



[0374] Into a 1000-mL round-bottom flask, was placed benzyl 4-(((1S,3r,5R)-3-(5-cyclopropylisoxazole-3-carboxamido)-8-aza-bicyclo[3.2.1]octan-8-ylsulfonyl)methyl)piperidine-1-carboxylate (48 g, 86.23 mmol, 1.00 equiv), hydrochloric acid (12 N, 500 mL). The resulting solution was stirred for 8 h at 25°C. The resulting mixture was concentrated under vacuum. This resulted in 39 g (99%) of 5-cyclopropyl-N-((1S,3r,5R)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide hydrochloride as an off-white solid. LCMS (method A, ESI): RT= 0.99 min, m/z=423.0[M+H]$^+$

Step 6: Synthesis of 5-cyclopropyl-N-((1*S*,3*r*,5*R*)-8-((1-methylpiperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide



[0375] In Into a 2000-mL round-bottom flask, was placed 5-cyclopropyl-N-((1S,3r,5R)-8-(piperidin-4-ylmethylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide hydrochloride (42 g, 91.50 mmol, 1.00 equiv), methanol (800 mL), formaldehyde (40 mL), acetic acid (8 mL). The resulting solution was stirred for 0.5 h at 25°C. This was followed by the addition of sodium cyanoborohydride (11 g, 175.05 mmol, 2.00 equiv) in several batches at 0°C. The resulting solution was stirred for 2 h at 25°C. The resulting mixture was concentrated under vacuum. The pH value of the solution was adjusted to 10 with sodium hydroxide (1 N). The resulting solution was extracted with 2x500 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate. The resulting mixture was concentrated under vacuum. This resulted in 38.9 g (98%) of 5-cyclopropyl-N-((1S,3r,5R)-8-((1-methylpiperidin-4-yl)methylsulfonyl)-8-aza-bicyclo[3.2.1]octan-3-yl)isoxazole-3-carboxamide as an off-

white solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 6.41(s, 1H), 4.28-4.18 (m, 3H), 3.10(d, *J*=6.0 Hz, 2H), 2.94(d, *J*=12.0 Hz, 2H), 2.34-1.95(m, 17H), 1.60-1.40(m, 2H), 1.21-1.15(m, 2H), 1.05-0.98(m, 2H) *ppm*. LCMS (method B, ESI): RT=1.64 min, m/z=437.1$[M+H]^+$.

EXAMPLE 30

SMYD3 Biochemical Assay

General Materials

[0376] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Tris, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^{3}H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well opaque white OptiPlates and SPA beads (Perkin Elmer, catalog # RPNQ0013) were purchased from PerkinElmer.

Substrates

[0377] N-terminally GST-tagged MEKK2 (MAP3K2) protein corresponding to reference sequence AAF63496.3 was purchased from Life Technologies (catalog # PV4010). This protein was expressed in High Five insect cells and purified to >85 % purity. Protein identity was confirmed by MS/MS analysis after proteolytic digestion. The protein sequence used was:

MAPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNK
KFELGLEFPNLPYYIDGDVKLTQSMAIIRYIADKHNMLGGCPKERA
EISMLEGAVLDIRYGVSRIAYSKDFETLKVDFLSKLPEMLKMFEDR
LCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCF
KKRIEAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLVPRH
NQTSLYKKAGTMDDQQALNSIMQDLAVLHKASRPALSLQETRKA
KSSSPKKQNDVRVKFEHRGEKRILQFPRPVKLEDLRSKAKIAFGQS
MDLHYTNNELVIPLTTQDDLDKALELLDRSIHMKSLKILLVINGST
QATNLEPLPSLEDLDNTVFGAERKKRLSIIGPTSRDRSSPPPGYIPDE
LHQVARNGSFTSINSEGEFIPESMEQMLDPLSLSSPENSGSGSCPSL
DSPLDGESYPKSRMPRAQSYPDNHQEFSDYDNPIFEKFGKGGTYPR
RYHVSYHHQEYNDGRKTFPRARRTQGNQLTSPVSFSPTDHSLSTSS

GSSIFTPEYDDSRIRRRGSDIDNPTLTVMDISPPSRSPRAPTNWRLG
KLLGQGAFGRVYLCYDVDTGRELAVKQVQFDPDSPETSKEVNAL
ECEIQLLKNLLHERIVQYYGCLRDPQEKTLSIFMEYMPGGSIKDQL
KAYGALTENVTRKYTRQILEGVHYLHSNMIVHRDIKGANILRDST
GNVKLGDFGASKRLQTICLSGTGMKSVTGTPYWMSPEVISGQGYG
RKADIWSVACTVVEMLTEKPPWAEFEAMAAIFKIATQPTNPKLPP
HVSDYTRDFLKRIFVEAKLRPSADELLRHMFVHYH.
(SEQ ID No. 1).

Molecular Biology

[0378] Full-length human SMYD3 isoform 1 (BAB86333) was inserted into a modified pET21b plasmid containing a His6 tag and TEV and SUMO cleavage sites. Because two common variants of SMYD3 exist in the population, site directed mutagenesis was subsequently performed to change amino acid 13 from an asparagine to a lysine, resulting in plasmid pEPZ533. A lysine at position 13 conforms to the more commonly occurring sequence (NP_001161212).

Protein Expression

[0379] *E. coli* (BL21 codonplus RIL strain, Stratagene) were transformed with plasmid pEPZ553 by mixing competent cells and plasmid DNA and incubating on ice for 30 minutes followed by heat shock at 42 °C for 1 minute and cooling on ice for 2 minutes. Transformed cells were grown and selected on LB agar with 100 μg/mL ampicillin and 17 μg/mL chloramphenicol at 37 °C overnight. A single clone was used to inoculate 200 mL of LB medium with 100 μg/mL ampicillin and 17 μg/mL chloramphenicol and incubated at 37 °C on an orbital shaker at 180 rpm. Once in log growth, the culture was diluted 1:100 into 2 L of LB medium and grown until OD_{600} was about 0.3 after which the culture was incubated at 15 °C and 160 rpm. Once OD_{600} reached about 0.4, IPTG was added to a final concentration of 0.1 mM and the cells were grown overnight at 15 °C and 160 rpm. Cells were harvested by centrifugation at 8000 rpm, for 4 minutes at 4 °C and stored at -80 °C for purification.

Protein Purification

[0380] Expressed full-length human His-tagged SMYD3 protein was purified from cell paste by Nickel affinity chromatography after equilibration of the resin with Buffer A (25 mM Tris, 200 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, pH7.8). The column was washed with Buffer B (Buffer A plus 20 mM imidazole) and His-tagged SMYD3

was eluted with Buffer C (Buffer A plus 300 mM imidazole). The His tag, TEV and SUMO cleavage sites were removed generating native SMYD3 by addition of ULP1 protein at a ratio of 1:200 (ULP1:SMYD3). Imidazole was removed by dialysis overnight in Buffer A. The dialyzed solution was applied to a second Nickel column and the native SMYD3 protein was collected from the column flow-through. The flow-through was dialyzed in Buffer D (25 mM Tris, 5% glycerol, 5 mM β-mercaptoethanol, 50 mM NaCl, pH7.8) and ULP1 was removed using a Q sepharose fast flow column. SMYD3 was eluted in Buffer A and further purified using an S200 size-exclusion column equilibrated with Buffer A. SMYD3 was concentrated to 2 mg/mL with a final purity of 89%.

Predicted Translation:

[0381] SMYD3 (Q9H7B4)

MEPLKVEKFATAKRGNGLRAVTPLRPGELLFRSDPLAYTVCKGSR
GVVCDRCLLGKEKLMRCSQCRVAKYCSAKCQKKAWPDHKRECK
CLKSCKPRYPPDSVRLLGRVVFKLMDGAPSESEKLYSFYDLESNIN
KLTEDKKEGLRQLVMTFQHFMREEIQDASQLPPAFDLFEAFAKVIC
NSFTICNAEMQEVGVGLYPSISLLNHSCDPNCSIVFNGPHLLLRAV
RDIEVGEELTICYLDMLMTSEERRKQLRDQYCFECDCFRCQTQDK
DADMLTGDEQVWKEVQESLKKIEELKAHWKWEQVLAMCQAIISS
NSERLPDINIYQLKVLDCAMDACINLGLLEEALFYGTRTMEPYRIFF
PGSHPVRGVQVMKVGKLQLHQGMFPQAMKNLRLAFDIMRVTHG
REHSLIEDLILLLEECDANIRAS. (SEQ ID No. 2).

General Procedure for SMYD3 Enzyme Assays on MEKK2 protein substrate

[0382] The assays were all performed in a buffer consisting of 25 mM Tris-Cl pH 8.0, 1 mM TCEP, 0.005% BSG, and 0.005% Tween 20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a 384-well white opaque OptiPlate using a Bravo automated liquid handling platform outfitted with a 384-channel head (Agilent Technologies). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of SMYD3, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD3 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD3 for 30 min at room temperature, then a cocktail (10ul) containing SAM and MEKK2 was added to

initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD3 was 0.4 nM, ^{3}H-SAM was 8 nM, MEKK2 was 12 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 100 uM, which dilutes the ^{3}H-SAM to a level where its incorporation into MEKK2 is no longer detectable. Radiolabeled MEKK2 was detected using a scintillation proximity assay (SPA). 10 uL of a 10 mg/mL solution of SPA beads in 0.5 M citric acid was added and the plates centrifuged at 600 rpm for 1 min to precipitate the radiolabeled MEKK2 onto the SPA beads. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^{3}H-labeled MEKK2 as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\%\ inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}}\right) \times 100$$

[0383] Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{\left(1 + \left(\frac{X}{IC_{50}}\right)^{Hill\ coefficient}\right.}$$

[0384] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

[0385] SMYD3 biochemical assay data for representative Compounds of the Disclosure are presented in Tables 1A, 2A, and 3A in the column titled "SMYD3Biochem IC_{50} (μM)."

EXAMPLE 31

SMYD3 Cell Assay

Trimethyl-MEKK2-In-Cell Western Assay

[0386] 293T/17 adherent cells were purchased from ATCC (American Type Culture Collection), Manassas, VA, USA. MEM/Glutamax medium, Optimem Reduced Serum medium, penicillin-streptomycin, 0.05% trypsin and 1x D-PBS were purchased from Life

Technologies, Grand Island, NY, USA. PBS-10X was purchased from Ambion, Life Technologies, Grand Island, New York, USA. PBS with Tween 20 (PBST (10x)) was purchased from KPL, Gaithersburg, Maryland,USA. Tet System FBS- approved FBS US Source was purchased from Clontech, Mountain View, California, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, 680CW Goat anti-mouse IgG (H+L) and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Tri-methyl-Lysine [A260]-MEKK2 antibody, MEKK2 and SMYD3 plasmids were made at Epizyme. Anti-flag monoclonal mouse antibody was purchased from Sigma, St. Louis, MO, USA. Methanol was purchased from VWR, Franklin, MA, USA. 10% Tween 20 was purchased from KPL, Inc., Gaithersburg, Maryland, USA. Fugene was purchased from Promega, Madison, WI, USA. The Biotek ELx405 was purchased from BioTek, Winooski, Vermont, USA. The multidrop combi was purchased from Thermo Scientific, Waltham, Massachusetts, USA.

[0387] 293T/17 adherent cells were maintained in growth medium (MEM/Glutamax medium supplemented with 10% v/v Tet System FBS and cultured at 37 °C under 5% CO_2.

Cell treatment, In Cell Western (ICW) for detection of trimethyl-lysine-MEKK2 and MEKK2.

[0388] 293T/17 cells were seeded in assay medium at a concentration of 33,333 cells per cm^2 in 30 mL medium per T150 flask and incubated at 37 °C under 5% CO_2. Plasmids were prepared for delivery to cells by first mixing 1350 µL Opti-MEM with Fugene (81 µL) in a sterile Eppendorf and incubated for five minutes at room temperature (RT). MEKK2-flag (13.6 ug/T150) MEKK2 p3XFlag-CMV-14 with C-3XFlag and SMYD3 (0.151 ug/T150) SMYD3 p3XFlag-CMV-14 without C-3XFlag plasmids were aliquotted to a 1.7 mL sterile microfuge tube. The gene ID for MEKK2 and SMYD3 is NM_006609.3 and Q9H7B4, respectively. Entire volume of Opti-MEM/Fugene mixture was then added to a microfuge tube containing DNA plasmid, mixed and then incubated x 15 minutes at RT. The medium on the 293T/17 cells was refreshed, and the DNA/Fugene complex is added aseptically to each flask, rocked gently, and incubated at 37 C for 5 hours. Medium was then removed, and cells were washed once with PBS in the flask. Trypsin 0.05% (3mL) was added and cells incubated for three minutes. Room temperature MEM+10% Tet system FBS was added and cells were mixed gently, and counted using the Vi-cell. Cells were seeded at 100,000 cells/mL in 50 µL

MEM/10%Tet FBS/Pen/Strep to a 384 well black/clear poly-D-lysine coated plate containing test agent diluted in DMSO. The final top concentration of test compound was 40 μM. The total concentration of DMSO did not exceed 0.2% (v/v). Plates were incubated x 30 minutes at RT in low-airflow area, followed by incubation at 37 °C under 5% CO_2 for 24 hours. Medium was aspirated from all wells of assay plates prior to fixation and permeabilization with ice cold (-20 °C) methanol (90 μL/well) for ten minutes. Plates were rinsed with PBS three times on BioTek ELx405. PBS was removed with a final aspiration, and Odyssey blocking buffer (50 μL/well) was added to each well and incubated for one hour at RT. Primary antibody solution was prepared (anti-trimethyl-MEKK2 at 1:600 dilution plus mouse anti-flag antibody at 1:10,000 dilution in diluent (Odyssey Blocking buffer + 0.1% Tween 20)) and 20 μL per well was dispensed using the Multidrop Combi. Assay plates were then sealed with foil, and incubated overnight at 4° C. Plates were washed five times with PBS-Tween (1X) on Biotek ELx405 and blotted on paper towel to remove excess reagent. Detection antibody solution (IRDye 800 CW goat anti-rabbit IgG diluted 1:400 in diluent (Odyssey Blocking buffer + 0.1% Tween 20), plus IRDye 680CW goat anti-mouse IgG at 1:500 in diluent (Odyssey Blocking buffer + 0.1% Tween 20) was added (20 μL/well) and incubated in dark for one hour at RT. Plates were then washed four times with PBS-T (1X) on ELx405. A final rinse with water was performed (115 μL/well x three washes on the ELx405). Plates were then centrifuged upside down, on paper towel, at 200 x g to remove excess reagent. Plates were left to dry in dark for one hour. The Odyssey Imager was used to measure the integrated intensity of 700 and 800 wavelengths at resolution of 84 μm, medium quality, focus offset 4.0, 700 channel intensity = 3.5 to measure the MEKK2-flag signal, 800 channel intensity = 5 to measure the Trimethyl-MEKK2 signal of each well.

Calculations:

[0389] First, the ratio for each well was determined by:

$$\left(\frac{\text{Trimethyl MEKK2 800nm value}}{\text{flag tagged MEKK2 700nm value}}\right)$$

[0390] Each plate included fourteen control wells of DMSO only treatment (Minimum Inhibition) as well as fourteen control wells for maximum inhibition (Background). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially

diluted two-fold in DMSO for a total of nine test concentrations, beginning at 40 μM. Percent inhibition was calculated (below).

$$\text{Percent Inhibition} = 100-\left(\left(\frac{(\text{Individual Test Sample Ratio})-(\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio})-(\text{Background Average Ratio})}\right)*100\right)$$

[0391] Non-linear regression curves were generated to calculate the IC_{50} and dose-response relationship using triplicate wells per concentration of compound.

[0392] SMYD3 cell assay data for representative Compounds of the Disclosure are presented in Tables 1A, 2A, and 3A in the column titled "SMYD3 Cell IC_{50} (μM)."

EXAMPLE 32

SMYD2 ASSAY

General Materials

[0393] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^{3}H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

Substrates

[0394] Peptide was synthesized with a N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-perfomance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was ARTKQTARKSTGGKAPRKQLATKAARKSA(K-Biot)-amide. (SEQ ID NO:3)

Production of Recombinant SMYD2 Enzymes for Biochemical Enzyme Activity Assays

[0395] Full length SMYD2 (NP_064582.2) was cloned into a pFastbac-Htb-lic vector with an N-terminal His6 *tag* and *FLAG tag*, preceded by a *TEV* protease *cleavage* site. The protein was expressed in Sf9 insect cells. Cells were resuspended in lysis buffer (25 mM HEPES-NaOH, pH 7.5, 200 mM NaCl, 5% glycerol, and 5 mM β-ME) and lysed by sonication. The protein was purified by Ni-NTA (Qiagen), followed by TEV cleavage to remove the His6 tag, subtractive Ni-NTA (Qiagen), and gel filtration chromatography

using an S200 column (GE Healthcare). Purified protein was stored in 20 mM Tris-HCl, pH 8.0, 100 mM NaCl, and 1 mM TCEP.

General Procedure for SMYD2 Enzyme Assays on Peptide Substrates

[0396] The assays were all performed in a buffer consisting of 20mM Bicine (pH=7.6), 1mM TCEP, 0.005% Bovine Skin Gelatin, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of SMYD2, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD2 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD2 for 30 min at room temperature, then a cocktail (10ul) containing ^{3}H-SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD2 was 1.5nM, ^{3}H-SAM was 10nM, and peptide was 60nM, SAH in the minimum signal control wells was 1000uM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radioactive SAM (10ul) to a final concentration of 600uM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1%Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\%\ inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}}\right) \times 100$$

[0397] Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$\%\ inhibition = Bottom + \frac{Top - Bottom}{(1 + (IC_{50}/[I])^{Hill\ coefficient})}$$

[0398] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. *I* is the compound concentration.

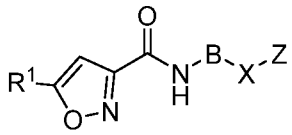
[0399] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof.

[0400] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0401] All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What is Claimed Is:

1. A compound having Formula **I**:

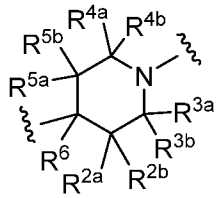


I

or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

B is:



;

X is selected from the group consisting of $-S(=O)_2-$, $S(=O)_2N(R^7)-$, $-S(=O)_2C(R^8)(H)-$, $-C(=O)-$, $-C(=O)N(R^7)-$, $-C(=O)O-$, $-C(=O)C(R^8)(H)-$, and $-S(=O)_2N(R^7)C(=O)N(R^{11})-$; or X is absent;

wherein the sulfur atom of $-S(=O)_2N(R^7)-$, $-S(=O)_2C(R^8)(H)-$, or $-S(=O)_2N(R^7)C(=O)N(R^{11})-$ is attached to the nitrogen atom of B, the carbon atom of $-C(=O)N(R^7)-$ or $-C(=O)O-$ is attached to the nitrogen atom of B, and the carbonyl carbon atom of $-C(=O)C(R^8)(H)-$ is attached the nitrogen atom of B;

Z is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, fluoroalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, [(cycloalkyl)alkylamino]alkyl, [(heterocyclo)alkylamino]alkyl, alkoxyalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and heteroaralkyl;

R^1 is selected from the group consisting of ethyl, n-propyl, isopropyl, isobutyl, and cyclopropyl;

R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{5a} and R^{5b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{2a} and R^{5a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{3a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{2a} and R^{4a} taken together form a C_{1-4} bridge; and R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{3a} and R^{5a} taken form a C_{1-4} bridge; and R^{2a}, R^{2b}, R^{3b}, R^{4a}, R^{4b}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

R^6 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^7 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and $-N(R^9)C(=O)R^{10}$;

R^9 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^{10} is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, and

R^{11} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

with the proviso that said compound having Formula I is not:

5-cyclopropyl-N-(piperidin-4-yl)isoxazole-3-carboxamide;

N-(8-azabicyclo[3.2.1]octan-3-yl)-5-cyclopropylisoxazole-3-carboxamide;

N-(1-(2-amino-2-oxoethyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

5-cyclopropyl-N-(1-(methylsulfonyl)piperidin-4-yl)isoxazole-3-carboxamide;

N-(1-benzylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

5-cyclopropyl-N-(1-isobutyrylpiperidin-4-yl)isoxazole-3-carboxamide;

N-(1-benzoylpiperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

ethyl 4-(5-cyclopropylisoxazole-3-carboxamido)piperidine-1-carboxylate;

5-cyclopropyl-N-(1-(furan-3-carbonyl)piperidin-4-yl)isoxazole-3-carboxamide;

5-cyclopropyl-N-(1-((4-methoxyphenyl)sulfonyl)piperidin-4-yl)isoxazole-3-carboxamide;

5-cyclopropyl-N-(1-tosylpiperidin-4-yl)isoxazole-3-carboxamide;

5-cyclopropyl-N-(1-(2,6-dimethylpyrimidin-4-yl)piperidin-4-yl)isoxazole-3-carboxamide;

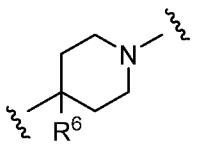
N-(1-((4-acetamidophenyl)sulfonyl)piperidin-4-yl)-5-cyclopropylisoxazole-3-carboxamide;

5-cyclopropyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide;

N-(1-(7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)piperidin-4-yl)-5-ethylisoxazole-3-carboxamide; or

5-ethyl-N-(1-(4-isopropyl-5-(pyridin-4-yl)pyrimidin-2-yl)piperidin-4-yl)isoxazole-3-carboxamide.

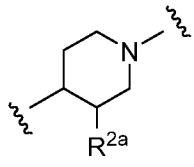
2. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



3. The compound of claim 2, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^6 is selected from the group consisting of hydrogen and methyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^6 is hydrogen.

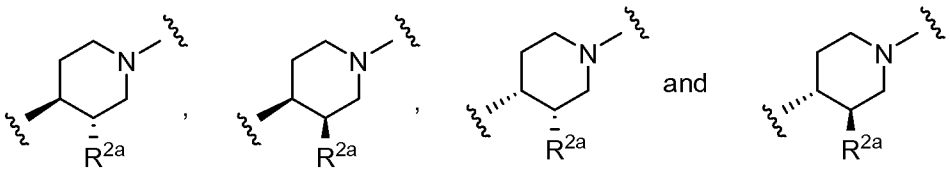
5. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



;

and R^{2a} is selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl.

6. The compound of claim 5 or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:

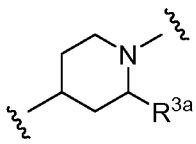


and

.

7. The compound of claims 5 or 6, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} is selected from the group consisting of methyl, ethyl, phenyl, $-CH_2Ph$, $-CF_3$, $-CO_2Et$, and $-CH_2OH$.

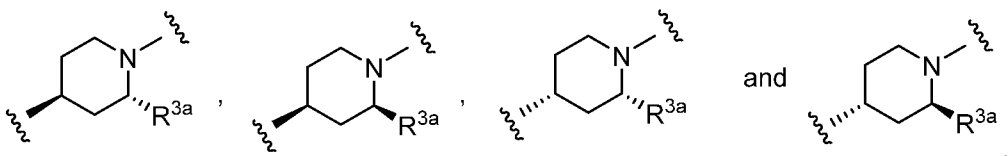
8. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



;

and R^{3a} is selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:

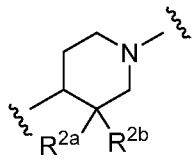


and

.

10. The compound of claims 8 or 9, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, *tert*-butyl, phenyl, and $-CH_2Ph$.

11. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:

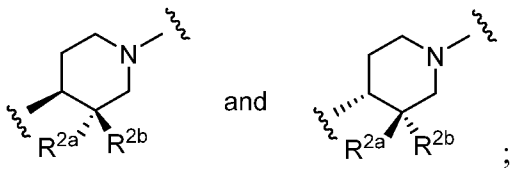


;

and R^{2a} and R^{2b} are each independently selected from the group consisting of halo and C_{1-6} alkyl; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

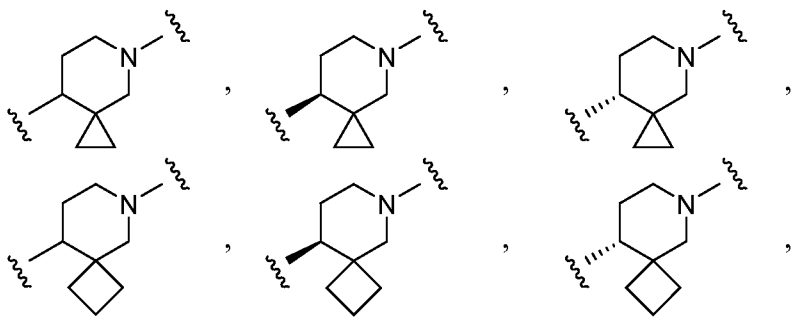
12. The compound of claim 11, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:

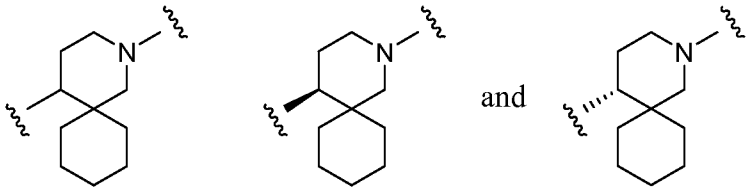


;

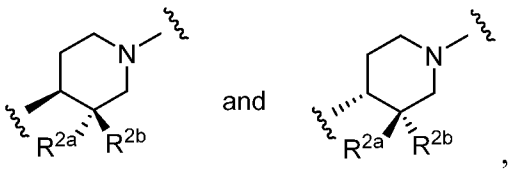
R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

13. The compound of claims 11 or 12, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:





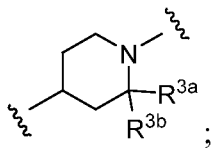
14. The compound of claim 11, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



and R^{2a} and R^{2b} are each independently selected from the group consisting of halo and C_{1-4} alkyl.

15. The compound of claims 11 or 14, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} and R^{2b} are selected from the group consisting of fluoro and methyl.

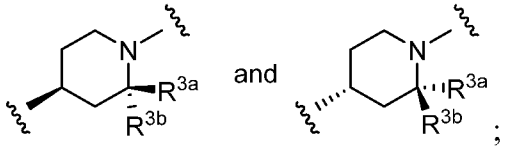
16. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



R^{3a} and R^{3b} are each independently selected from the group consisting of halo and C_{1-6} alkyl; or

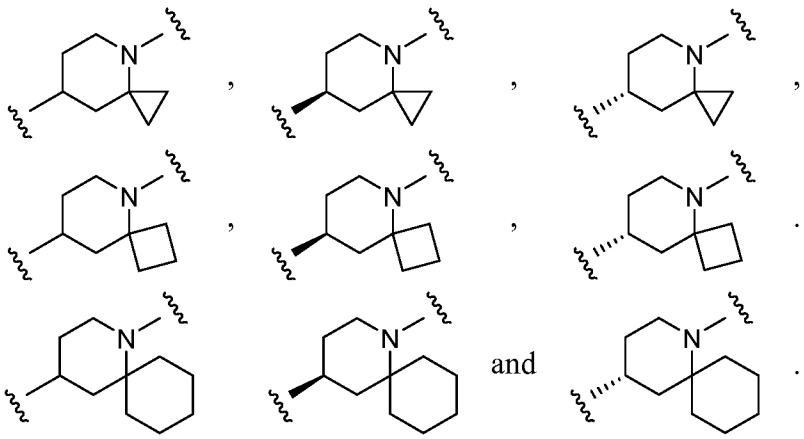
R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

17. The compound of claim 16, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:

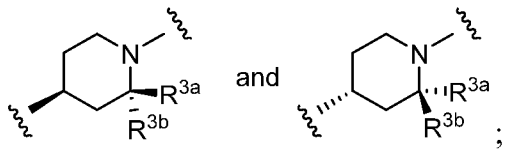


and R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

18. The compound of claims 16 or 17, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



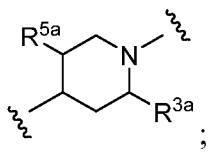
19. The compound of claim 16, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



and R^{3a} and R^{3b} are each independently selected from the group consisting of halo and C_{1-4} alkyl.

20. The compound of claims 16 or 19, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} and R^{3b} are selected from the group consisting of fluoro and methyl.

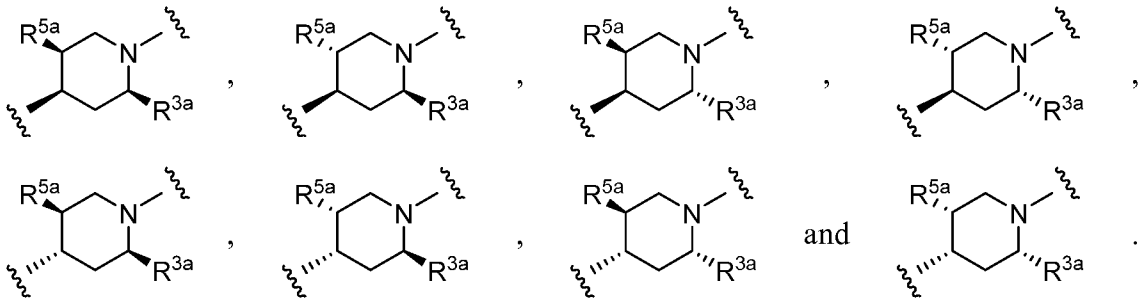
21. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is :



R^{3a} and R^{5a} are each independently C_{1-6} alkyl; or

R^{3a} and R^{5a} taken together form a C_{1-4} bridge.

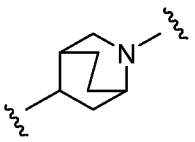
22. The compound of claim 21, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



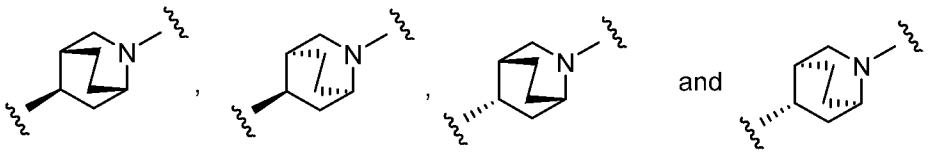
23. The compound of claim 22, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} and R^{5a} are each independently C_{1-4} alkyl.

24 The compound of claim 23, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} and R^{5a} are each methyl or ethyl.

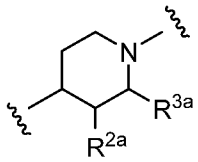
25. The compound of claim 21, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



26. The compound of claim 25, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:

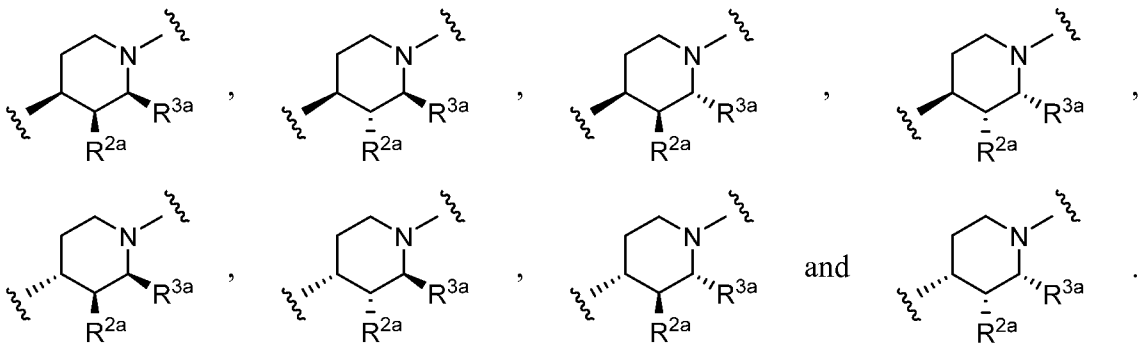


27. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



wherein R^{2a} and R^{3a} are each independently C_{1-6} alkyl.

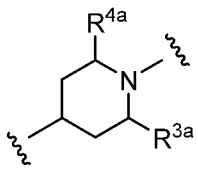
28. The compound of claim 27, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



29. The compound of claim 28, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} and R^{3a} are each independently C_{1-4} alkyl.

30. The compound of claim 29, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} and R^{3a} are each methyl or ethyl.

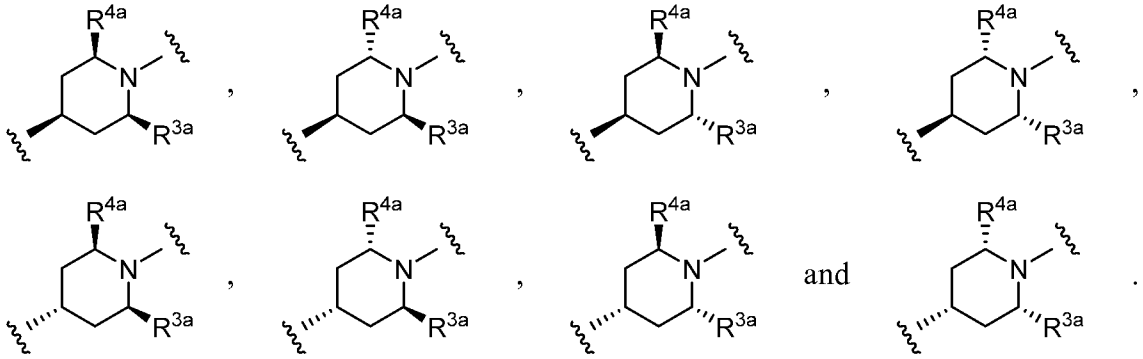
31. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



wherein R^{3a} and R^{4a} are each independently C_{1-6} alkyl; or

R^{3a} and R^{4a} taken together form a C_{1-4} bridge.

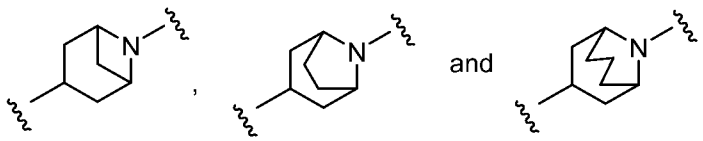
32. The compound of claim 31, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



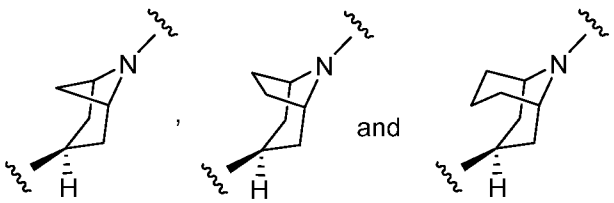
33. The compound of claim 32 or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} and R^{4a} are each independently C_{1-4} alkyl.

34. The compound of claim 33, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{3a} and R^{4a} are each methyl or ethyl.

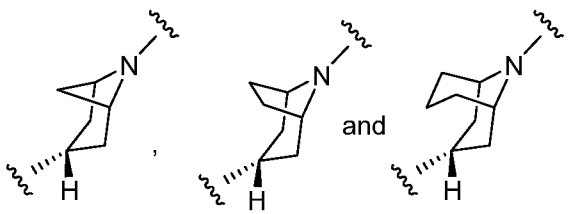
35. The compound of claim 34, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



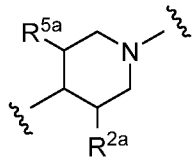
36. The compound of claim 35, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



37. The compound of claim 35, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



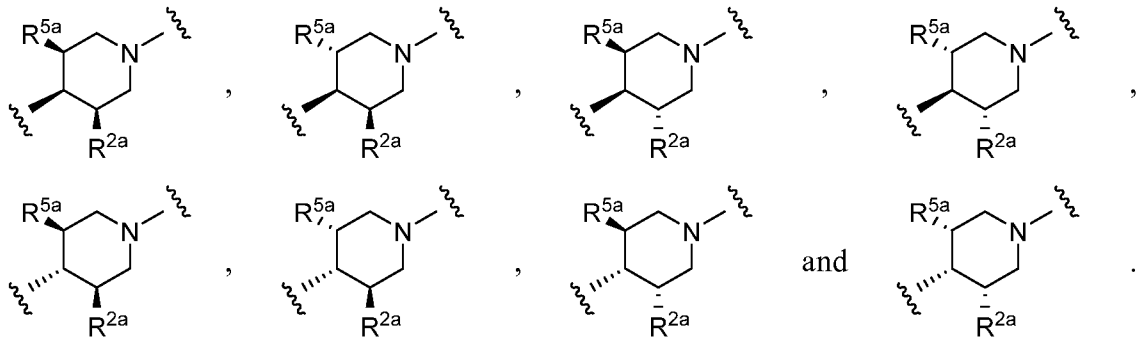
38. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



wherein R^{2a} and R^{5a} are each independently selected from the group consisting of C_{1-6} alkyl and alkoxycarbonyl; or

R^{2a} and R^{5a} taken together form a C_{1-4} bridge.

39. The compound of claim 38, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is:



40. The compound of claim 39, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} and R^{5a} are each independently selected from the group consisting of C_{1-4} alkyl and alkoxycarbonyl.

41. The compound of claim 40, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{2a} and R^{5a} are each independently selected from the group consisting of methyl and $-CO_2Me$.

42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is $-S(=O)_2-$.

43. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is -C(=O)-.

44. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is absent.

45. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is $-S(=O)_2N(H)-$.

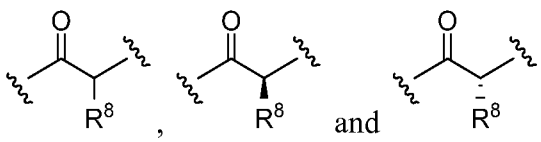
46. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is -C(=O)N(H)-.

47. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is -C(=O)O-.

48. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is $-S(=O)_2CH_2-$.

49. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is $-C(=O)CH_2-$.

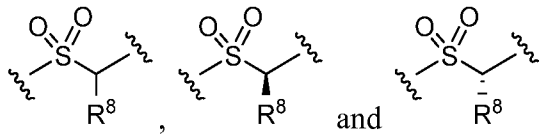
50 The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is selected from the group consisting of:



; and

R^8 is selected from the group consisting of C_{1-4} alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and $-N(R^9)C(=O)R^{10}$.

51. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or hydrate thereof, wherein X is selected from the group consisting of:



; and

R^8 is selected from the group consisting of C_{1-4} alkyl, amino, alkylamino, dialkylamino, cycloalkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, hydroxyalkyl, and $-N(R^9)C(=O)R^{10}$.

52. The compound of claims 50 or 51, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^8 is selected from the group consisting of $-NH_2$, $-CH_2NH_2$, and $-N(H)C(=O)R^{10}$.

53. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, (aralkylamino)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, and optionally substituted C_{3-12} cycloalkyl.

54. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein one or more of R^{2a}, R^{3a}, R^{4a}, and R^{5a} is independently selected from the group consisting of halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl.

55. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^6 is C_{1-4} alkyl.

56. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein:

R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{3-12} cycloalkyl, haloalkyl, hydroxyalkyl, optionally substituted C_{6-14} aryl, aralkyl, and alkoxycarbonyl; or

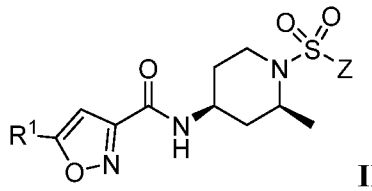
R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{5a}, and R^{5b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or

R^{5a} and R^{5b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl; and R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl.

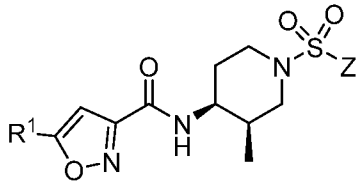
57. The compound of claim 1 having Formula **III**:



III

or a pharmaceutically acceptable salt or hydrate thereof.

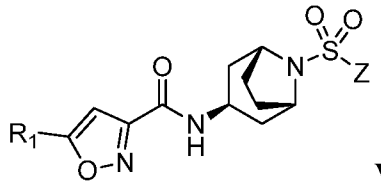
58. The compound of claim 1 having Formula **IV**:



IV

or a pharmaceutically acceptable salt or hydrate thereof.

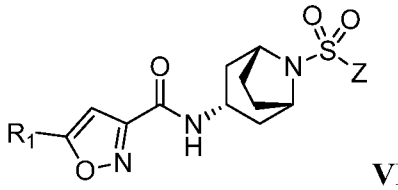
59. The compound of claim 1 having Formula **V**:



V

or a pharmaceutically acceptable salt or hydrate thereof.

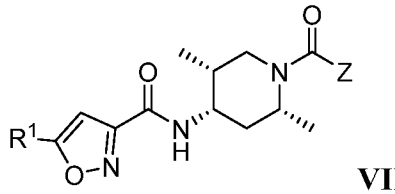
60. The compound of claim 1 having Formula **VI**:



VI

or a pharmaceutically acceptable salt or hydrate thereof.

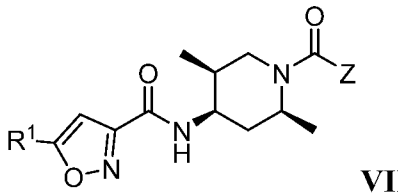
61. The compound of claim 1 having Formula **VII**:



VII

or a pharmaceutically acceptable salt or hydrate thereof.

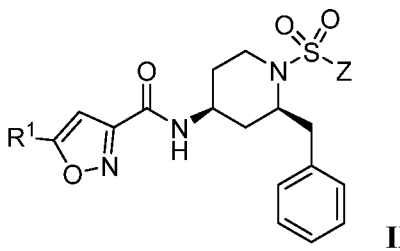
62. The compound of claim 1 having Formula **VIII**:



VIII

or a pharmaceutically acceptable salt or hydrate thereof.

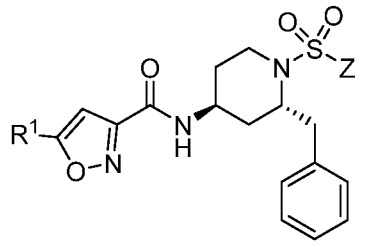
63. The compound of claim 1 having Formula **IX**:



IX

or a pharmaceutically acceptable salt or hydrate thereof.

64. The compound of claim 1 having Formula X:



X

or a pharmaceutically acceptable salt or hydrate thereof.

65. The compound of any one of claims 1-64, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is ethyl.

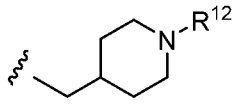
66. The compound of any one of claims 1-64, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is cyclopropyl.

67. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, and optionally substituted 4- to 14-membered heterocyclo.

68. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of (heterocyclo)alkyl, (amino)alkyl-susbstituted phenyl, amino-substituted piperidine, alkylamino-substituted piperidine, dialkylamino-substituted piperidine, and amino-substituted cyclohexyl.

69. The compound of any one of claims 1-68, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is (heterocyclo)alkyl.

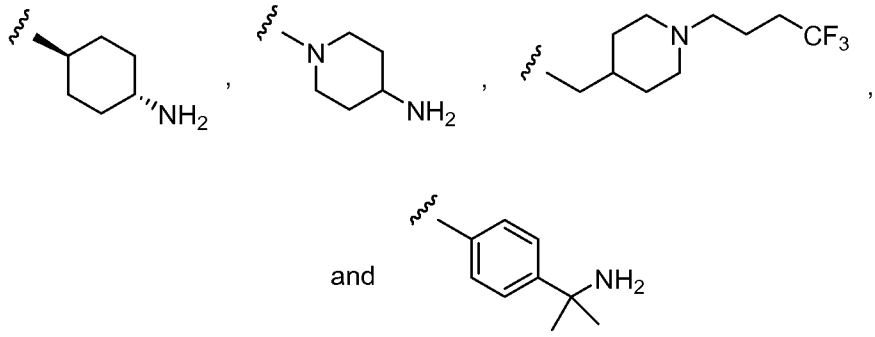
70. The compound of claim 69, or a pharmaceutically acceptable salt or hydrate thereof, wherein said (heterocyclo)alkyl is:


; and

R^{12} is selected from the group consisting of hydrogen, fluoroalkyl, hydroxyalkyl, aralkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

71. The compound of claim 70, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{12} is selected from the group consisting of hydrogen, fluoroalkyl, hydroxyalkyl, aralkyl, alkyl, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl

72. The compound of any one of claims 1-68, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is selected from the group consisting of:


and

.

73. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, selected from any one or more of the compounds provided in Table 1, Table 1A, Table 2, Table 2A, Table 3, or Table 3A of the specification.

74. A pharmaceutical composition comprising the compound of any one of claims 1-73, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

75. A method of treating a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-73, or a pharmaceutically acceptable salt or hydrate thereof, wherein the patient has cancer.

76. The method of claim 75, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer,

MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

77. The pharmaceutical composition of claim 74 for use in treating cancer.

78. The pharmaceutical composition of claim 77, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic

carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue

neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

79. A compound of any one of claims 1-73, or a pharmaceutically acceptable salt or hydrate thereof, for use in treatment of cancer.

80. The compound of claim 79, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma,

astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary

tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

81. Use of a compound of any one of claims 1-73, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for treatment of cancer.

82. The use of claim 81, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma,

choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis,

seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

83. A kit comprising the compound of any one of claims 1-73, or a pharmaceutically acceptable salt or hydrate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or hydrate thereof, to a patient having cancer.

84. The kit of claim 83, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm,

endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous

carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

85. A method of treating a SMYD protein mediated disorder comprising administering to a subject in need thereof a compound of any one of claims 1-73, or a pharmaceutically acceptable salt or hydrate thereof in an effective amount to treat the SMYD protein mediated disorder.

SEQUENCE LISTING

<110> EPIZYME, INC.
Mitchell, Lorna H
Bell, Andrew S
Chesworth, Richard
Foley, Megan A
Kuntz, Kevin W
Mills, James E
Munchhof, Michael J

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        35                  40                  45

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    50                  55                  60

Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80

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Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
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225                 230                 235                 240

Gln Ala Leu Asn Ser Ile Met Gln Asp Leu Ala Val Leu His Lys Ala
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Ser Arg Pro Ala Leu Ser Leu Gln Glu Thr Arg Lys Ala Lys Ser Ser
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Ser Pro Lys Lys Gln Asn Asp Val Arg Val Lys Phe Glu His Arg Gly
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Glu Lys Arg Ile Leu Gln Phe Pro Arg Pro Val Lys Leu Glu Asp Leu
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Ile Leu Leu Val Ile Asn Gly Ser Thr Gln Ala Thr Asn Leu Glu Pro
        355                 360                 365

Leu Pro Ser Leu Glu Asp Leu Asp Asn Thr Val Phe Gly Ala Glu Arg
    370                 375                 380
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```
Lys Lys Arg Leu Ser Ile Ile Gly Pro Thr Ser Arg Asp Arg Ser Ser
385                 390                 395                 400

Pro Pro Pro Gly Tyr Ile Pro Asp Glu Leu His Gln Val Ala Arg Asn
                405                 410                 415

Gly Ser Phe Thr Ser Ile Asn Ser Glu Gly Glu Phe Ile Pro Glu Ser
            420                 425                 430

Met Glu Gln Met Leu Asp Pro Leu Ser Leu Ser Ser Pro Glu Asn Ser
        435                 440                 445

Gly Ser Gly Ser Cys Pro Ser Leu Asp Ser Pro Leu Asp Gly Glu Ser
    450                 455                 460

Tyr Pro Lys Ser Arg Met Pro Arg Ala Gln Ser Tyr Pro Asp Asn His
465                 470                 475                 480

Gln Glu Phe Ser Asp Tyr Asp Asn Pro Ile Phe Glu Lys Phe Gly Lys
                485                 490                 495

Gly Gly Thr Tyr Pro Arg Arg Tyr His Val Ser Tyr His His Gln Glu
            500                 505                 510

Tyr Asn Asp Gly Arg Lys Thr Phe Pro Arg Ala Arg Arg Thr Gln Gly
        515                 520                 525

Asn Gln Leu Thr Ser Pro Val Ser Phe Ser Pro Thr Asp His Ser Leu
    530                 535                 540

Ser Thr Ser Ser Gly Ser Ser Ile Phe Thr Pro Glu Tyr Asp Asp Ser
545                 550                 555                 560

Arg Ile Arg Arg Arg Gly Ser Asp Ile Asp Asn Pro Thr Leu Thr Val
                565                 570                 575

Met Asp Ile Ser Pro Pro Ser Arg Ser Pro Arg Ala Pro Thr Asn Trp
            580                 585                 590

Arg Leu Gly Lys Leu Leu Gly Gln Gly Ala Phe Gly Arg Val Tyr Leu
        595                 600                 605

Cys Tyr Asp Val Asp Thr Gly Arg Glu Leu Ala Val Lys Gln Val Gln
    610                 615                 620

Phe Asp Pro Asp Ser Pro Glu Thr Ser Lys Glu Val Asn Ala Leu Glu
625                 630                 635                 640

Cys Glu Ile Gln Leu Leu Lys Asn Leu Leu His Glu Arg Ile Val Gln
                645                 650                 655
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```
Tyr Tyr Gly Cys Leu Arg Asp Pro Gln Glu Lys Thr Leu Ser Ile Phe
            660                 665                 670

Met Glu Tyr Met Pro Gly Gly Ser Ile Lys Asp Gln Leu Lys Ala Tyr
        675                 680                 685

Gly Ala Leu Thr Glu Asn Val Thr Arg Lys Tyr Thr Arg Gln Ile Leu
    690                 695                 700

Glu Gly Val His Tyr Leu His Ser Asn Met Ile Val His Arg Asp Ile
705                 710                 715                 720

Lys Gly Ala Asn Ile Leu Arg Asp Ser Thr Gly Asn Val Lys Leu Gly
                725                 730                 735

Asp Phe Gly Ala Ser Lys Arg Leu Gln Thr Ile Cys Leu Ser Gly Thr
            740                 745                 750

Gly Met Lys Ser Val Thr Gly Thr Pro Tyr Trp Met Ser Pro Glu Val
        755                 760                 765

Ile Ser Gly Gln Gly Tyr Gly Arg Lys Ala Asp Ile Trp Ser Val Ala
    770                 775                 780

Cys Thr Val Val Glu Met Leu Thr Glu Lys Pro Pro Trp Ala Glu Phe
785                 790                 795                 800

Glu Ala Met Ala Ala Ile Phe Lys Ile Ala Thr Gln Pro Thr Asn Pro
                805                 810                 815

Lys Leu Pro Pro His Val Ser Asp Tyr Thr Arg Asp Phe Leu Lys Arg
            820                 825                 830

Ile Phe Val Glu Ala Lys Leu Arg Pro Ser Ala Asp Glu Leu Leu Arg
        835                 840                 845

His Met Phe Val His Tyr His
    850                 855


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Gly Leu Arg Ala Val Thr Pro Leu Arg Pro Gly Glu Leu Leu Phe Arg
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            20                  25                  30

Ser Asp Pro Leu Ala Tyr Thr Val Cys Lys Gly Ser Arg Gly Val Val
        35                  40                  45

Cys Asp Arg Cys Leu Leu Gly Lys Glu Lys Leu Met Arg Cys Ser Gln
    50                  55                  60

Cys Arg Val Ala Lys Tyr Cys Ser Ala Lys Cys Gln Lys Lys Ala Trp
65                  70                  75                  80

Pro Asp His Lys Arg Glu Cys Lys Cys Leu Lys Ser Cys Lys Pro Arg
                85                  90                  95

Tyr Pro Pro Asp Ser Val Arg Leu Leu Gly Arg Val Val Phe Lys Leu
            100                 105                 110

Met Asp Gly Ala Pro Ser Glu Ser Glu Lys Leu Tyr Ser Phe Tyr Asp
        115                 120                 125

Leu Glu Ser Asn Ile Asn Lys Leu Thr Glu Asp Lys Lys Glu Gly Leu
    130                 135                 140

Arg Gln Leu Val Met Thr Phe Gln His Phe Met Arg Glu Glu Ile Gln
145                 150                 155                 160

Asp Ala Ser Gln Leu Pro Pro Ala Phe Asp Leu Phe Glu Ala Phe Ala
                165                 170                 175

Lys Val Ile Cys Asn Ser Phe Thr Ile Cys Asn Ala Glu Met Gln Glu
            180                 185                 190

Val Gly Val Gly Leu Tyr Pro Ser Ile Ser Leu Leu Asn His Ser Cys
        195                 200                 205

Asp Pro Asn Cys Ser Ile Val Phe Asn Gly Pro His Leu Leu Leu Arg
    210                 215                 220

Ala Val Arg Asp Ile Glu Val Gly Glu Glu Leu Thr Ile Cys Tyr Leu
225                 230                 235                 240

Asp Met Leu Met Thr Ser Glu Glu Arg Arg Lys Gln Leu Arg Asp Gln
                245                 250                 255

Tyr Cys Phe Glu Cys Asp Cys Phe Arg Cys Gln Thr Gln Asp Lys Asp
            260                 265                 270

Ala Asp Met Leu Thr Gly Asp Glu Gln Val Trp Lys Glu Val Gln Glu
        275                 280                 285

Ser Leu Lys Lys Ile Glu Glu Leu Lys Ala His Trp Lys Trp Glu Gln
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290 295 300

Val Leu Ala Met Cys Gln Ala Ile Ile Ser Ser Asn Ser Glu Arg Leu
305 310 315 320

Pro Asp Ile Asn Ile Tyr Gln Leu Lys Val Leu Asp Cys Ala Met Asp
325 330 335

Ala Cys Ile Asn Leu Gly Leu Leu Glu Glu Ala Leu Phe Tyr Gly Thr
340 345 350

Arg Thr Met Glu Pro Tyr Arg Ile Phe Phe Pro Gly Ser His Pro Val
355 360 365

Arg Gly Val Gln Val Met Lys Val Gly Lys Leu Gln Leu His Gln Gly
370 375 380

Met Phe Pro Gln Ala Met Lys Asn Leu Arg Leu Ala Phe Asp Ile Met
385 390 395 400

Arg Val Thr His Gly Arg Glu His Ser Leu Ile Glu Asp Leu Ile Leu
405 410 415

Leu Leu Glu Glu Cys Asp Ala Asn Ile Arg Ala Ser
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1 5 10 15

Arg Lys Gln Leu Ala Thr Lys Ala Ala Arg Lys Ser Ala
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