BICYCLIC HETEROCYCLIC AMIDE INHIBITORS OF $Na_V1.8$ FOR THE TREATMENT OF PAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of Indian Patent Application No. 202311013223, filed February 27, 2023, which claims the benefit of Indian Patent Application No. 202211024240, filed April 25, 2022, each of which is incorporated by reference herein in its entirety.

FIELD

[0002] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions in treating conditions associated with voltage-gated sodium channel function, in particular $Na_V1.8$, for example pain and conditions associated with pain. Also provided herein are methods of treating pain in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject.

BACKGROUND

[0003] Voltage-gated sodium channels are large integral membrane protein complexes present in neurons and excitable tissues where they contribute to processes such as membrane excitability and muscle contraction (Ogata et al., *Jpn. J. Pharmacol.* (2002) 88(4) 365-77). They have been identified as a primary target for the treatment of pain. Genes encoding for nine distinct mammalian isoforms of Na_V channels (Na_V isoforms 1.1-1.9) have been sequenced. Variation in the gating properties of different Na_V isoforms, cellular distributions, and expression levels influence the physiology of nerve cell conduction. A mounting body of evidence suggests that individual Na_V isoforms Na_V 1.3, 1.7, 1.8 and 1.9 are disproportionately involved in pain signaling and nociception, and that an isoform-specific inhibitor of Na_V could provide pain relief without the accompanying undesirable effects of a non-specific Na_V antagonist or an opioid drug (Momin et al., *Curr Opin Neurobiol.* 18(4): 383-8, 2008; Rush et al., *J. Physiol.* 579(Pt 1): 1-14, 2007).

[0004] $Na_V1.8$ is selectively expressed in dorsal root ganglion (DRG) neurons, a type of pseudo-unipolar neuron that project both centrally and peripherally, which are implicated in nociception. As a result of its sensory neuron specificity, $Na_V1.8$ is particularly important in

the pathophysiology of pain. The design of a drug which selectively inhibits Na_V 1.8 over the other Na_V channels is therefore desirable. Such a drug design is challenging given the high structural homology (75-96%) of the mammalian Na_V isoforms.

[0005] Isoform-selective selective inhibitors have been sought by a number of research groups and certain compounds have advanced to clinical development. Isoform-selective small molecule inhibitors of Na_V 1.8 are disclosed in the following patent applications and publications: WO 2021/257490; WO 2021/257418; WO 2021/257420; WO 2021/113627; WO 2021/032074; WO 2020/261114; WO 2020/219867; WO 2020/146682; WO 2020/092187; WO 2020/092667; WO 2020/014246; WO 2020/014243; WO 2019/157505; WO 2019/014352; WO 2018/213426; WO 2015/089361; WO 2015/010065; WO 2014/120820; WO 2014/120815; WO 2014/120808; WO 2013/114250; WO 2013/061205; WO 2008/135830; Brown et al., *Bioorg Med Chem.* 27(1):230-239, 2019; Bagal et al., *Med Chem Comm*. 7(10), 2016; Bagal et al., *ACS Med Chem Lett.* 6(6):650-654, 2015; Jarvis et al., *PNAS* 104(20):8520-8525, 2007.

[0006] Previous efforts to develop isoform-selective inhibitors of Na_V 1.8 as human therapeutics have encountered a number of challenges. These include insufficient selectivity over off-target human Na_V 1.x isoforms, limited target engagement *in vivo* (due to insufficient potency for human Na_V1.8, high protein or tissue binding, state-dependent inhibition of Na_V 1.8, safety concerns that preclude dose escalation, or a combination thereof), physico-chemical properties such as poor solubility that impeded oral dosing, and compound-specific issues such as toxicological findings or formation of metabolites that could pose safety risks to humans. Certain compounds also exhibit species variation in Na_V 1.8 potency (see e.g. Bagal et al., *Med Chem Comm*. 7(10), 2016) such that it is challenging to evaluate their on-target pharmacodynamic effects in standard preclinical species *i.e.* mouse and rat.

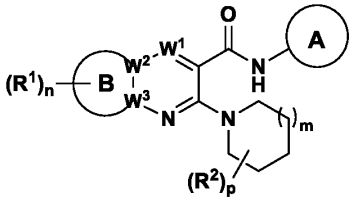
[0007] There exists a need for compounds which treat pain and conditions associated with voltage-gated sodium channel function, particularly which selectively inhibit Na_V 1.8 over other Na_V isoforms.

SUMMARY

[0008] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions for the treatment of conditions modulated by voltage-gated sodium channels,

in particular, Na_V 1.8, and in some or any embodiments, in the treatment of pain. Also provided herein are methods of treating pain and/or conditions modulated by voltage-gated sodium channels in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject. In some or any embodiments, the subject is a human.

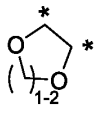
[0009] In one aspect, provided herein is a compound of Formula (**I**):

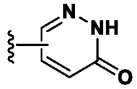
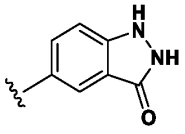
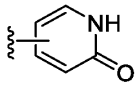


(**I**)

wherein

$\mathbf{R^1}$, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$;  optionally substituted with $(R^{3a})_{q1}$;  optionally substituted with $(R^{3a})_{q1}$; or  optionally substituted with $(R^{3a})_{q1}$;

W^1 is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C_1-C_6 alkoxy)=;

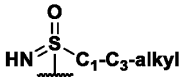
W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R^2, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or

two R^2 are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two R^2 are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

R^3 is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -C(=NH)NH_2, -C(O)NH_2, -NH_2, -NHC(O)$C_{1\text{-}3}$alkyl, -NHC(O)NH_2, -$NHS(O)_2NH_2$, -NHC(=NH)NH_2, -$S(O)_2$NH**R**, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5cycloalkyl; where the C_3-C_6cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

provided that the compound is not

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

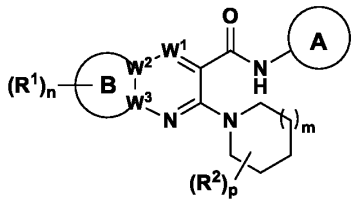
2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

or 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[0010] In another aspect, provided herein is a compound of Formula (**I-P2**):

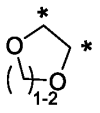


(I-P2)

wherein

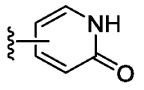
R1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two **R1** are attached on adjacent ring carbons in 

, and together with the adjacent carbons to which they are attached form 

, where * indicate the

shared carbons in  and any remaining **R**[1] are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; or  optionally substituted with $(R^{3a})_{q1}$;

W[1] is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

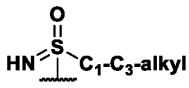
W[2] and **W**[3] are each -C-, the dashed bond between **W**[2] and **W**[3] is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of **W**[2] and **W**[3] is -C- and the other is -N-, the dashed bond between **W**[2] and **W**[3] is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R[2], independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R**[2] are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R**[2], independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R**[2] are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R**[2], independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

R[3] is hydrogen, -OH, -B(OH)$_2$, -COOH, hydroxyalkyl, -C(=NH)NH$_2$, -C(O)NH$_2$, -NH$_2$, -NHC(O)C_{1-3}alkyl, -NHC(=NH)NH$_2$, -S(O)$_2$NH**R**, -S(O)$_2$$C_1$-$C_6$-alkyl, amino-$C_1$-$C_6$alkyl, halo-$C_1$-$C_3$alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with

one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

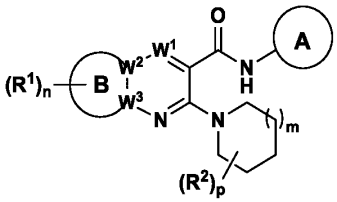
p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

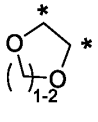
[0011] In another aspect, provided herein is a Compound of Formula (**I-P1**):

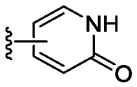


(**I-P1**)

wherein

$\mathbf{R^1}$, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; or  optionally substituted with $(\mathbf{R^{3a}})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

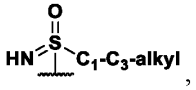
$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

$\mathbf{R^3}$ is hydrogen, -C(O)NH_2, -NH_2, -S(O)$_2$NH**R**, -S(O)$_2$$C_1$-$C_6$-alkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl or C_3-C_5 cycloalkyl;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3; or

a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[0012] In a further aspect, provided herein is a compound according to any one of the following formulas:

<table>
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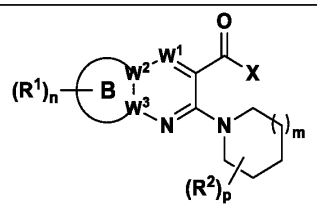
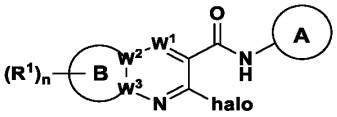
<td>
(A)
where X is OH, OCH_3, OCH_2CH_3, or NH_2;</td>
<td>
(B);</td>
</tr>
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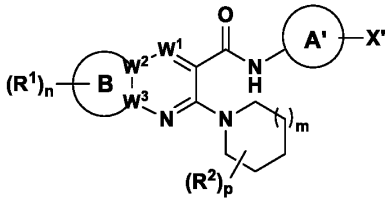
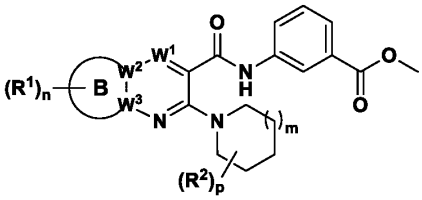
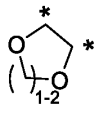
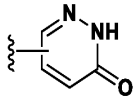
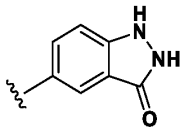
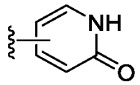
<td>
(C)
where X′ is SCH_3 or $S(O)CH_3$; and A′ is phenyl or pyridinyl; and</td>
<td>
(D);</td>
</tr>
</table>

wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two **R^1** are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining **R^1** are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with **R^3** and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with **R^3** and optionally substituted with $(R^{3a})_q$; 

optionally substituted with $(R^{3a})_{q1}$;  optionally substituted with $(R^{3a})_{q1}$; or  optionally substituted with $(\mathbf{R^{3a}})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C_1-C_6 alkoxy)=;

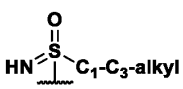
$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

$\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -C(=NH)NH_2, -C(O)NH_2, -NH_2, -NHC(O)$C_{1\text{-}3}$alkyl, -NHC(O)NH_2, -NHS(O)$_2NH_2$, -NHC(=NH)NH_2, -S(O)$_2$NH**R**, -S(O)$_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered

heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

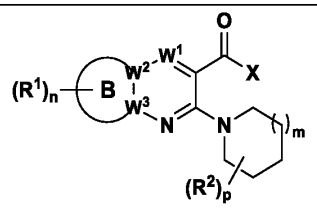
n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, 4, 5, or 6

q1 is 0, 1, or 2; and

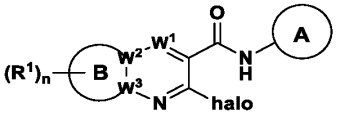
q is 0, 1, 2, or 3.

[0013] In a further aspect, provided herein is a compound according to any one of the following formulas:

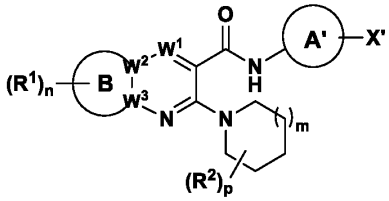


(A)

where **X** is OH, OCH_3, OCH_2CH_3, or NH_2;

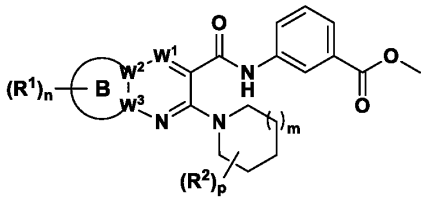


(B);



(C)

where **X′** is SCH_3 or $S(O)CH_3$; and **A′** is phenyl or pyridinyl; and

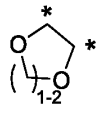


(D);

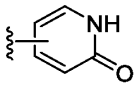
or a salt thereof,

wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two R^1 are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in

 and any remaining **R**^{1} are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$; 5- to 10-membered heteroaryl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$; or  optionally substituted with (**R**^{3a})$_{q1}$;

W^{1} is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

W^{2} and **W**^{3} are each -C-, the dashed bond between **W**^{2} and **W**^{3} is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of **W**^{2} and **W**^{3} is -C- and the other is -N-, the dashed bond between **W**^{2} and **W**^{3} is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R^{2}, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R**^{2} are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R**^{2}, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two **R**^{2} are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R**^{2}, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

m is 0, 1, 2, or 3;

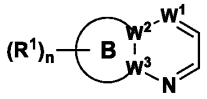
n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

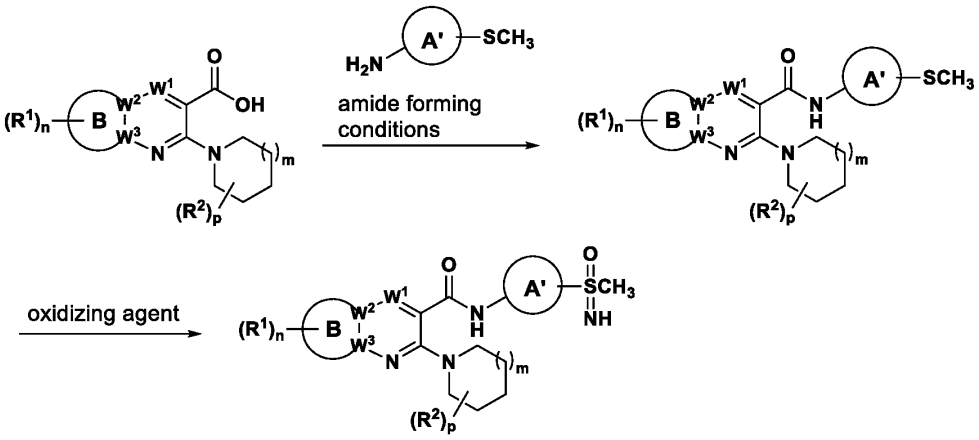
q is 0, 1, 2, or 3.

[0014] Additional embodiments are where **R**^{1} is as provided in Embodiments 1-1c or 17-17a; **A** is as provided in Embodiments 2-2k; **W**^{1} is as provided in Embodiments 3, 3a, or 3b; **W**^{2} and **W**^{3} are as provided in Embodiments 4, 4a, 5, 5a, or 6; **R**^{2}, independently in each

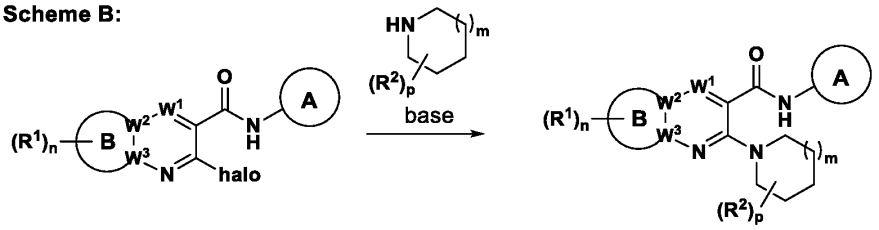
instance, is as provided in Embodiments 7-7c; $\mathbf{R^3}$ is as provided in Embodiments 8-8c; $\mathbf{R^{3a}}$ is as provided in Embodiment 9 or 9a; m, n, p, q, and q1 are as provided in Embodiments 10, 11, 12, 13, and 14, respectively; and  is as provided in Embodiments 15, 15a, 15b, 15c, 15d, 15e, 16, 16a, 16b, and 16c; and any combinations thereof.

[0015] In an additional aspect, provided herein is a method of preparing a compound disclosed herein according to any of the following schemes:

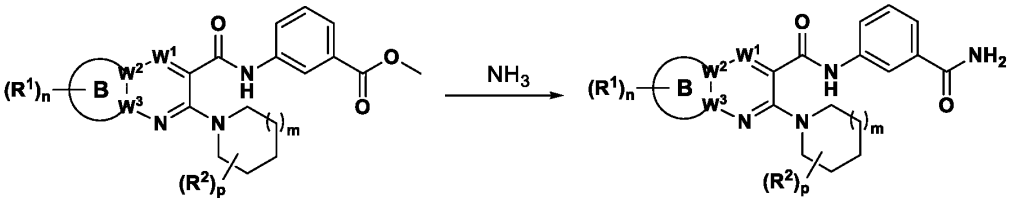
Scheme A:

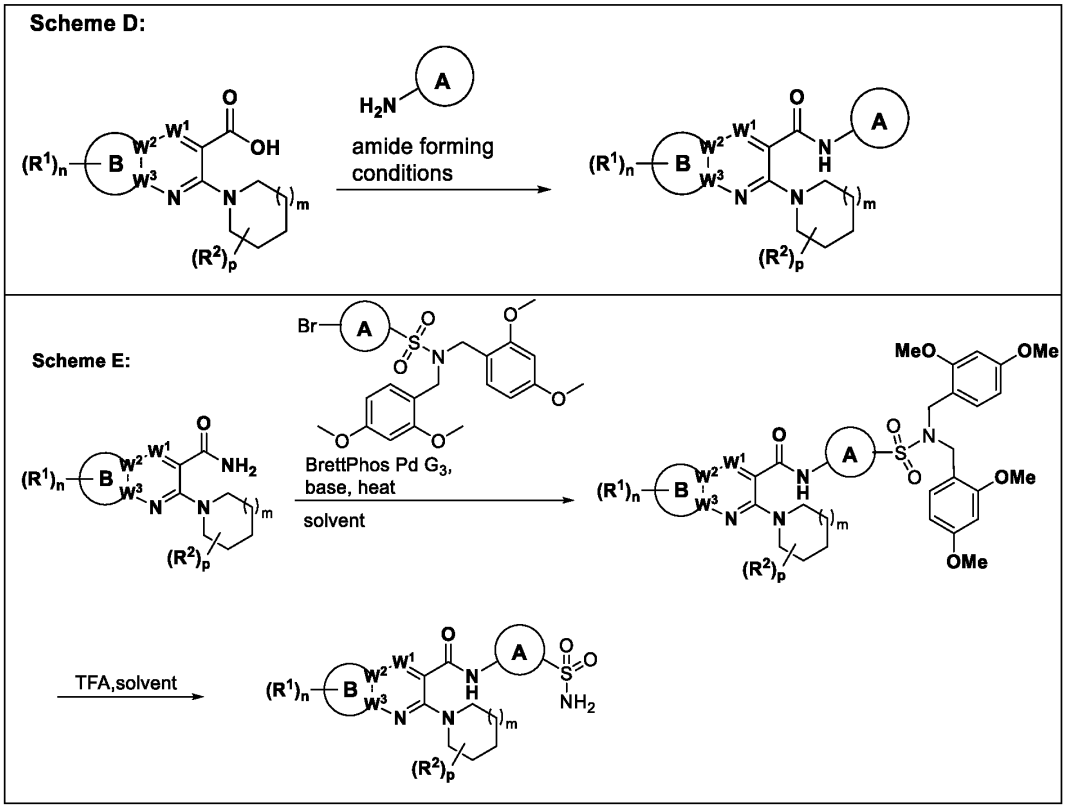


Scheme B:



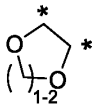
Scheme C:

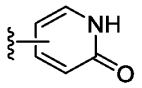




wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two **R**^{1} are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining **R**^{1} are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; or  optionally substituted with $(\mathbf{R^{3a}})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C1-C6 alkoxy)=;

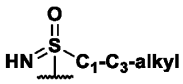
$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

$\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -C(=NH)NH_2, -C(O)NH_2, -NH_2, -NHC(O)$C_{1\text{-}3}$alkyl, -NHC(O)NH_2, -$NHS(O)_2NH_2$, -NHC(=NH)NH_2, -$S(O)_2$NH**R**, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

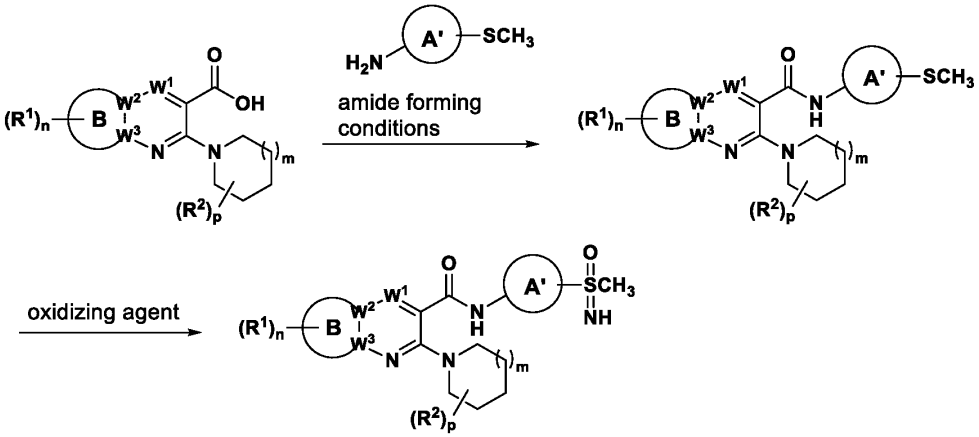
q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

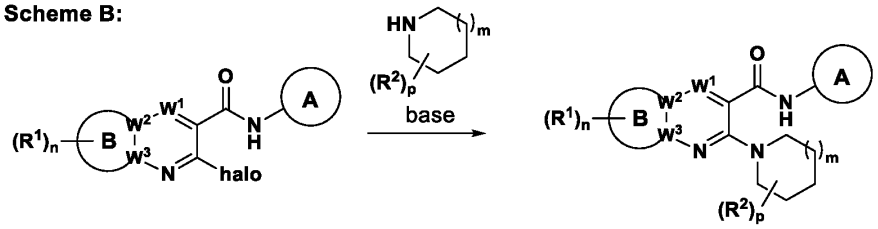
to yield the compound disclosed herein, or a pharmaceutically acceptable salt thereof and/or an isomer thereof; and optionally isolating the compound disclosed herein.

[0016] In an additional aspect, provided herein is a method of preparing a compound disclosed herein according to any of the following schemes:

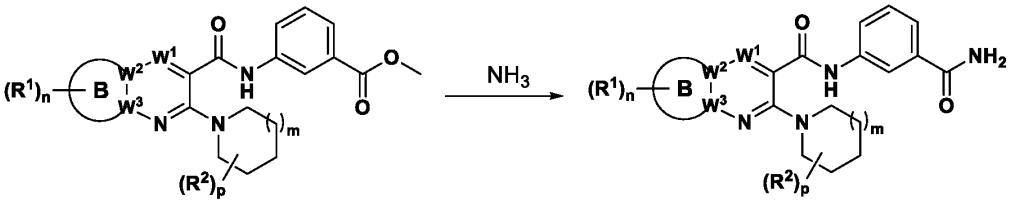
Scheme A:

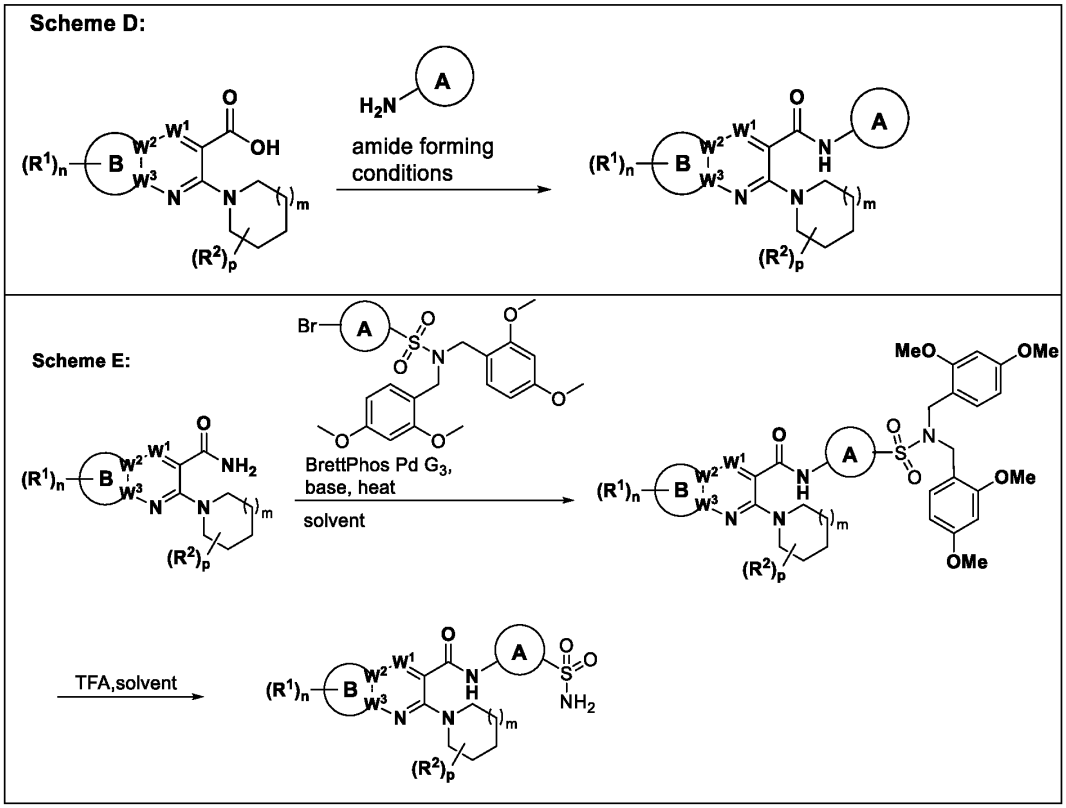


Scheme B:



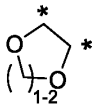
Scheme C:

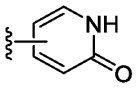




wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two **R**^{1} are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining **R**^{1} are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; or  optionally substituted with $(\mathbf{R^{3a}})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; ;

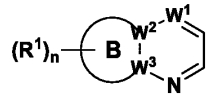
m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

to yield a compound disclosed herein; and optionally isolating the compound disclosed herein.

[0017] Additional embodiments are where $\mathbf{R^1}$ is as provided in Embodiments 1-1c or 17-17a; **A** is as provided in Embodiments 2-2k; $\mathbf{W^1}$ is as provided in Embodiments 3, 3a, or 3b; $\mathbf{W^2}$ and $\mathbf{W^3}$ are as provided in Embodiments 4, 4a, 5, 5a, or 6; $\mathbf{R^2}$, independently in each instance, is as provided in Embodiments 7-7c; $\mathbf{R^3}$ is as provided in Embodiments 8-8c; $\mathbf{R^{3a}}$ is as provided in Embodiment 9 or 9a; m, n, p, q, and q1 are as provided in Embodiments 10, 11,

12, 13, and 14, respectively; and  is as provided in Embodiments 15, 15a, 15b, 15c, 15d, 15e, 16, 16a, 16b, and 16c; and any combinations thereof.

[0018] In another aspect provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating pain and/or conditions modulated by voltage-gated sodium channels which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Formula (**I**), (**I-P1**), (**I-P2**), and compounds 151, 56, 59, 60, 82, 116, 119, and 169-206.

[0019] In another aspect provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating pain and/or conditions modulated by voltage-gated sodium channels which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), (**I-P2**), and compounds 1-127 and 169-206.

[0020] In another aspect provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating pain and/or conditions modulated by voltage-gated sodium channels which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), and compounds 1-206.

[0021] In an aspect, a method of treatment of condition associated with voltage-gated sodium channels function, including $Na_V1.8$, in a subject is provided comprising administering to an individual in need thereof a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), (**I-P1**), (**I-P2**), and compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206.

[0022] In an aspect, a method of treatment of condition associated with voltage-gated sodium channels function, including $Na_V1.8$, in a subject is provided comprising administering to an individual in need thereof a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), (**I-P2**), and compounds 1-127 and 169-206.

[0023] In an aspect, a method of treatment of condition associated with voltage-gated sodium channels function, including $Na_V1.8$, in a subject is provided comprising administering to an individual in need thereof a therapeutically or prophylactically effective amount of a

compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), and compounds 1-206.

[0024] In another aspect, provided is a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), (**I-P1**), (**I-P2**), and compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206, or a therapeutically or prophylactically effective amount of a pharmaceutical composition for use in treating a condition associated with voltage-gated sodium channels function, including $Na_v1.8$, in a subject in need thereof.

[0025] In another aspect, provided is a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**), (**I-P2**), and compounds 1-127 and 169-206, or a therapeutically or prophylactically effective amount of a pharmaceutical composition for use in treating a condition associated with voltage-gated sodium channels function, including $Na_v1.8$, in a subject in need thereof.

[0026] In another aspect, provided is a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (**I**) and compounds 1-206, or a therapeutically or prophylactically effective amount of a pharmaceutical composition for use in treating a condition associated with voltage-gated sodium channels function, including $Na_v1.8$, in a subject in need thereof.

BRIEF DESCRIPTION OF FIGURES

[0027] Fig. 1 depicts voltage protocols for a new test procedure (Protocol A).

[0028] Fig. 2 depicts voltage protocols for a new test procedure (Protocol B).

DETAILED DESCRIPTION

[0029] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions in the treatment of pain and/or conditions modulated by voltage-gated sodium channels, in particular Na_V 1.8. Also provided herein are methods of treating pain in a subject comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a subject. In an embodiment, the subject is a human.

Definitions

[0030] When referring to the compounds provided herein, the following terms have the following meanings unless indicated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. Unless specified otherwise, where a term is defined as being substituted, the groups in the list of substituents are themselves unsubstituted. For example, a substituted alkyl group can be substituted, for example, with a cycloalkyl group, and the cycloalkyl group is not further substituted unless specified otherwise.

[0031] Reference to "about" a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X". As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with temperatures, doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 15%, within 10%, within 5%, within 4%, within 3%, within 2%, within 1%, or within 0.5% of the specified dose, amount, or weight percent.

[0032] The terms "a" or "an," as used in herein means one or more, unless context clearly dictates otherwise.

[0033] The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In some or any embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In some or any embodiments, the alkyl group includes one to ten carbon atoms, *i.e.,* C_1 to C_{10} alkyl. In some or any embodiments, the alkyl is a $C_{1\text{-}6}$alkyl. In some or any embodiments, the alkyl group is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, *t*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

[0034] The term "hydroxyalkyl" as used herein, unless otherwise specified, refers to an alkyl, as defined herein, comprising an alcohol (hydroxy). In one or more embodiments, the alcohol group is a primary, secondary, or tertiary alcohol. In one or more embodiments, the

hydroxyalkyl group includes one to ten carbons, *i.e.*, C_1 to C_{10} hydroxyalkyl. In one or more embodiments, the hydroxyalkyl group includes one or two alcohol (hydroxy) groups, provided that they are not on the same carbon. In one or more embodiments, the hydroxyalkyl group is hydroxyC_{1-3}alkyl. In one or more embodiments, the hydroxyalkyl group is selected from the group consisting of hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl. In one or more embodiments, the hydroxyalkyl group is a C_{1-6}hydroxyalkyl. In one or more embodiments, the hydroxyalkyl group is selected from the group consisting of hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropan-2-yl, and 2-hydroxypropan-2-yl.

[0035] The term "alkoxy" and "alkyloxy" as used herein, and unless otherwise specified, refer to the group –OR′ where R′ is alkyl. Alkoxy and alkyloxy groups include, in some or any embodiments, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexyloxy, 1,2-dimethylbutoxy, and the like. In some embodiments, alkoxy is C_{1-6}alkoxy.

[0036] The term "amino" means $–NH_2$.

[0037] The term "aryl," as used herein, and unless otherwise specified, refers to a monovalent C_6- C_{15} carbocyclic ring system which comprises at least one aromatic ring wherein the aryl ring system is mono, di, or tricyclic. The aryl may be attached to the main structure through any of its rings, *i.e.* any aromatic or nonaromatic ring. In some or any embodiments, the aryl group may be a bridged (where chemically feasible) or non-bridged, spirocyclic (where chemically feasible) or not spirocyclic, and/or fused or not fused multicyclic group. In some or any embodiments, aryl is phenyl, naphthyl, indanyl, fluorenyl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulenyl, or tetrahydronaphthyl. When aryl is substituted, it can be substituted on any ring, *i.e.* on any aromatic or nonaromatic ring comprised by aryl.

[0038] The term "C_3-C_{10}-cycloalkyl," as used herein, refers to a monovalent, saturated, monocyclic hydrocarbon or bicyclic (fused, bridged, or spirocyclic) ring. In some or any embodiments, the terms "fused cycloalkyl" and "spirocycloalkyl" are embodiments of the cycloalkyl group. In some or any embodiments, the cycloalkyl group includes three to six carbon atoms, *i.e.*, C_3 to C_6 cycloalkyl. In some or any embodiments, the cycloalkyl has 3, 4, or 5 (C_{3-5}); 3 or 4 (C_{3-4}); 3 (C_3); 4 (C_4); or 5 (C_5) carbon atoms. In some or any embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some or any embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, or cyclopentyl. In some or any

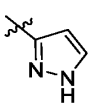
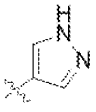
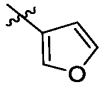
embodiments, the cycloalkyl group is cyclopropyl. In some or any embodiments, the cycloalkyl group is cyclobutyl. In some or any embodiments, the cycloalkyl group is cyclopentyl. In some or any embodiments, the cycloalkyl group is bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, or adamantyl.

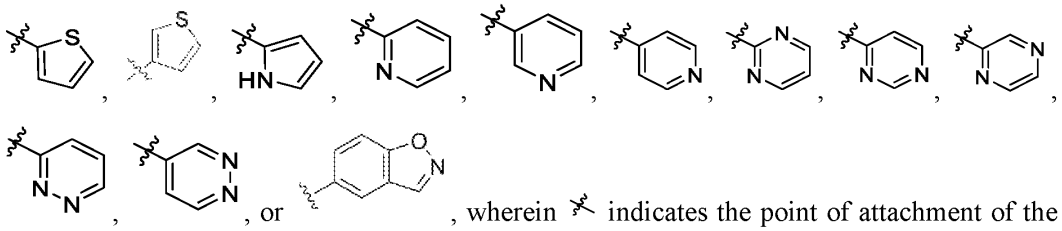
[0039] The term "cycloalkylalkyl" refers to an alkyl as defined herein, which is substituted by one or more than one cycloalkyl groups (which are independently selected) as defined herein. In some embodiments, "cycloalkylalkyl" is C_{3-8}cycloalkylC_{1-6}alkyl. In some embodiments, "cycloalkylalkyl" is alkyl substituted with one cycloalkyl. In some embodiments, cycloalkylalkyl is cyclopropylmethyl.

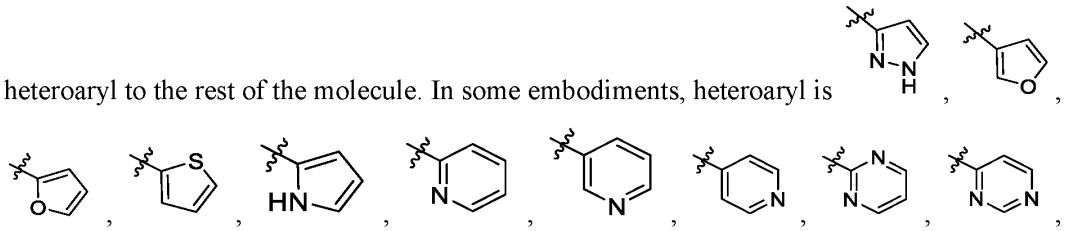
[0040] The term "haloalkyl," as used herein, and unless otherwise specified, refers to an alkyl group substituted with 1, 2, 3, 4, or 5 halo groups. In some or any embodiments, the haloalkyl is a halo-C_{1-6}alkyl. In some or any embodiments, the haloalkyl is $-CF_3$, $-CH_2F$, $-CHF_2$, or $-CH_2CF_3$.

[0041] The term "haloalkoxy," as used herein, and unless otherwise specified, refers to an -OR group where R is halo-C_{1-10}alkyl as defined herein. In some or any embodiments, the haloalkoxy is a halo-C_{1-6}alkoxy.

[0042] The terms "halogen" and "halo," as used herein, and unless otherwise specified, are synonymous and refer to chloro, bromo, fluoro or iodo.

[0043] The term "heteroaryl," as used herein, and unless otherwise specified, refers to a monocyclic aromatic ring system or multicyclic aromatic ring system wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the ring atoms is a heteroatom independently selected from O, $S(O)_{0-2}$, NH, and N, and the remaining ring atoms are carbon atoms, and where the ring may be optionally substituted as described herein. The heteroaryl group is bonded to the rest of the molecule through any atom in the ring system, valency rules permitting. In some or any embodiments, each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, or a combination thereof, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In some or any embodiments, the heteroaryl has from 5 to 20, from 5 to 15, from 5 to 6 ring atoms, or from 5 to 10 ring atoms. When heteroaryl is substituted, it can be substituted on any ring. In one or more embodiments, heteroaryl is , , , ,


, wherein indicates the point of attachment of the heteroaryl to the rest of the molecule. In some embodiments, heteroaryl is


, wherein indicates the point of attachment of the heteroaryl to the rest of the molecule.

[0044] In some or any embodiments, monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl and triazolyl. In some or any embodiments, bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzoisothiazolyl, benzothienyl, benzotriazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, or quinazolinyl. In some or any embodiments, tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, and phenazinyl. In some or any embodiments, heteroaryl is indolyl, furanyl, pyridinyl, pyrimidinyl, imidazolyl, or pyrazolyl; each of which is optionally substituted with 1, 2, 3, or 4 groups as defined throughout the specification, including in some embodiments with group(s) independently selected from $C_{1\text{-}6}$alkyl, hydroxy, halo, halo-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, cyano, or phenyl.

[0045] The term "heterocyclic," as used herein, and unless otherwise specified, refers to a monovalent monocyclic non-aromatic ring system or a monovalent multicyclic ring system

that contains at least one non-aromatic ring; wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of the monocyclic non-aromatic ring atoms is a heteroatom independently selected from O, $S(O)_{0-2}$, and N, and the remaining ring atoms are carbon atoms; and wherein one or more (in some or any embodiments, 1, 2, 3, or 4) of any of the ring atoms in the multicyclic ring system is a heteroatom(s) independently selected from O, $S(O)_{0-2}$, and N, and the remaining ring atoms are carbon. The term "heterocyclic" does not include fully aromatic ring(s), *i.e.* does not include imidazole, pyrimidine, pyridine, and the like. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are independently selected from nitrogen and oxygen. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are oxygen. In some or any embodiments, the heterocyclic ring comprises one or two heteroatom(s) which are nitrogen (where the nitrogen is substituted as described in any aspect or embodiment described herein). In some or any embodiments, heterocyclic is multicyclic and comprises one heteroatom in a non-aromatic ring, or comprises one heteroatom in an aromatic ring, or comprises two heteroatoms in an aromatic ring, or comprises two heteroatoms where one is in an aromatic ring and the other is in a non-aromatic ring. In some or any embodiments, the heterocyclic group has from 3 to 20, 3 to 15, 3 to 10, 3 to 8, 4 to 7, or 5 to 6 ring atoms. In some or any embodiments, the heterocyclic is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system. In some or any embodiments, the heterocyclic group may be a bridged or non-bridged, spirocyclic or not spirocyclic, and/or fused or not fused multicyclic group. One or more of the nitrogen and sulfur atoms may be optionally oxidized, one or more of the nitrogen atoms may be optionally quaternized, one or more of the carbon atoms may be optionally replaced with . Some rings may be partially or fully saturated, or aromatic provided that heterocyclic is not fully aromatic. The monocyclic and multicyclic heterocyclic rings may be attached to the main structure at any heteroatom or carbon atom which results in a stable compound. The multicyclic heterocyclic may be attached to the main structure through any of its rings, including any aromatic or nonaromatic ring, regardless of whether the ring contains a heteroatom. In some or any embodiments, heterocyclic is "heterocycloalkyl" which is 1) a saturated monovalent monocyclic group which contains at least one ring heteroatom, as described herein, or 2) a saturated monovalent bi- or tri-cyclic group in which at least one ring contains at least one heteroatom as described herein. When heterocyclic and heterocycloalkyl

are substituted, they can be substituted on any ring, i.e. on any aromatic or nonaromatic ring comprised by heterocyclic and heterocycloalkyl. In some or any embodiments, such heterocyclic includes, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, 1,3-dihydroisobenzofuranyl, benzofuranonyl, benzopyranonyl, benzopyranyl, dihydrobenzofuranyl, benzotetrahydrothienyl, 2,2-dioxo-1,3-dihydrobenzo[c]thienyl, benzothiopyranyl, benzoxazinyl, β-carbolinyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroquinolinyl, decahydroisoquinolinyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, 2,4-dioxo-imidazolidinyl, imidazolinyl, indolinyl, 2-oxo-indolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolinyl, 1-oxo-isoindolinyl, 1,3-dioxo-isoindolinyl, isothiazolidinyl, isoxazolidinyl, 3-oxo-isoxazolidinyl, morpholinyl, 3,5-dioxo-morpholinyl, octahydroindolyl, octahydroisoindolyl, 1-oxo-octahydroisoindolyl, 1,3-dioxo-hexahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, 2,6-dioxo-piperazinyl, piperidinyl, 2,6-dioxo-piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, 2-oxopyrrolidinyl, 2,5-dioxopyrrolidinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiomorpholinyl, 3,5-dioxo-thiomorpholinyl, thiazolidinyl, 2,4-dioxo-thiazolidinyl, tetrahydroquinolinyl, phenothiazinyl, phenoxazinyl, xanthenyl, and 1,3,5-trithianyl. In some or any embodiments, heterocyclic is benzo-1,4-dioxanyl, benzodioxolyl, indolinyl, 2-oxo-indolinyl, pyrrolidinyl, piperidinyl, 2,3-dihydrobenzofuranyl, or decahydroquinolinyl; each of which is optionally substituted with 1, 2, 3, or 4 groups as defined throughout the specification, including in some or any embodiments with group(s) independently selected from halo, alkyl, and phenyl. In some embodiments, heterocycloalkyl is pyrrolidinyl. In some embodiments, heterocycloalkyl is an N-linked heterocycloalkyl.

[0046] The term "oxo" as used herein and unless otherwise specified, refers to a keto group (C=O). An oxo group that is a substituent of a nonaromatic carbon results in a conversion of a $-CH_2-$ to -C=O. An oxo group that is a substituent of an aromatic carbon results in a conversion of -CH- to -C=O. When a substituent is oxo, then two hydrogens on the atom are replaced. When an oxo group substitutes aromatic moieties, the corresponding partially unsaturated ring

replaces the aromatic ring. For example, a pyridyl group substituted by an oxo group is a pyridone and a pyrimidinone. The person of ordinary skill in the art will appreciate that in some embodiments that such a group, e.g. pyridone, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, 3(2H)-oxo-pyridazinyl, and 3-oxo-1,2-dihydro-3H-indazolyl can exist in a tautomeric form, e.g. hydroxypyridine, 2,4-dihydroxypyrimidinyl, hydroxy-pyridazinyl, and 3-hydroxy-1H-indazolyl, respectively.

[0047] The term "protecting group," as used herein, and unless otherwise specified, refers to a group that is added to an oxygen, nitrogen or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. (See for example those described in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Fourth Edition, 2006, hereby incorporated by reference.)

[0048] The term "pharmaceutically acceptable salt," as used herein, and unless otherwise specified, refers to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise desirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, *tert*-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; and (2) base addition salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine,

diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N′-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, *N*-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

[0049] Pharmaceutically acceptable salts further include, in some or any embodiments, and without limitation, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium salts and the like. When the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, *e.g.* hydrochloride and hydrobromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, *tert*-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate and the like.

[0050] The term "substantially free of" or "substantially in the absence of" stereoisomers with respect to a composition refers to a composition that includes at least 85 or 90% by weight, in some or any embodiments 95%, 98%, 99% or 100% by weight, of a designated stereoisomer of a compound in the composition. In some or any embodiments, in the methods and compounds provided herein, the compounds are substantially free of stereoisomers.

[0051] Similarly, the term "isolated" with respect to a composition refers to a composition that includes at least 85, 90%, 95%, 98%, 99% to 100% by weight, of a specified compound, the remainder comprising other chemical species or stereoisomers.

[0052] The term "isotopic composition," as used herein, and unless otherwise specified, refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated,

when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural isotopic composition.

[0053] The term "isotopic enrichment," as used herein, and unless otherwise specified, refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. In some or any embodiments, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0054] The term "isotopically enriched," as used herein, and unless otherwise specified, refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

[0055] As used herein, the term "local anesthetic" means a drug which provides local numbness or pain relief. In some or any embodiments, local anesthetic includes aminoacylanilide compounds (in some or any embodiments, lidocaine, prilocaine, bupivacaine, ropivacaine, and mepivacaine) and related local anesthetic compounds having various substituents on the ring system or amine nitrogen; aminoalkyl benzoate compounds (in some or any embodiments, procaine, chloroprocaine, propoxycaine, hexylcaine, tetracaine, cyclomethycaine, benoxinate, butacaine, and proparacaine) and related local anesthetic compounds; cocaine; amino carbonate compounds (in some or any embodiments, diperodon); N-phenylamidine compounds (in some or any embodiments, phenacaine); N-aminoalkyl amide compounds (in some or any embodiments, dibucaine); aminoketone compounds (in some or any embodiments, falicaine and dyclonine); and amino ether compounds (in some or any embodiments, pramoxine and dimethisoquien).

[0056] As used herein, "alkyl," "hydroxyalkyl," "carbocyclic," "cycloalkyl," "aryl," "alkoxy," "heterocycloalkyl," and "heterocyclic" groups optionally comprise deuterium at one or more positions where hydrogen atoms are present, and wherein the deuterium composition of the atom or atoms is other than the natural isotopic composition.

[0057] Also as used herein, "alkyl," "hydroxyalkyl," "carbocyclic," "cycloalkyl," "aryl," "alkoxy," "heterocycloalkyl," "heterocyclic" groups optionally comprise carbon-13 at an amount other than the natural isotopic composition.

[0058] As used herein, and unless otherwise specified, the term "IC_{50}" refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response.

[0059] As used herein, the terms "subject" and "patient" are used interchangeably. The terms "subject" and "subjects" refer to an animal, such as a mammal including a non-primate (*e.g.*, a cow, pig, horse, cat, dog, rat, and mouse) and a primate (*e.g.*, a monkey such as a cynomolgous monkey, a chimpanzee and a human), and in some or any embodiments, a human. In some or any embodiments, the subject is a farm animal (*e.g.*, a horse, a cow, a pig, etc.) or a pet (*e.g.*, a dog or a cat). In some or any embodiments, the subject is a human.

[0060] As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment or prevention of a disorder or one or more symptoms thereof. In some or any embodiments, the term "therapeutic agent" includes a compound provided herein. In some or any embodiments, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment or prevention of a disorder or one or more symptoms thereof.

[0061] "Therapeutically effective amount" refers to an amount of a compound or composition that, when administered to a subject for treating a condition, is sufficient to effect such treatment for the condition. A "therapeutically effective amount" can vary depending on, *inter alia*, the compound, the condition and its severity, and the age, weight, *etc.*, of the subject to be treated.

[0062] "Treating" or "treatment" of any condition or disorder refers, in some or any embodiments, to ameliorating a condition or disorder that exists in a subject, including prophylactically. In another embodiment, "treating" or "treatment" includes ameliorating at least one physical parameter, which may be indiscernible by the subject. In yet another embodiment, "treating" or "treatment" includes modulating the condition or disorder, either physically (*e.g.,* stabilization of a discernible symptom) or physiologically (*e.g.,* stabilization of a physical parameter) or both. In yet another embodiment, "treating" or "treatment" includes delaying the onset of the condition or disorder. In yet another embodiment, "treating" or "treatment" includes the reduction or elimination of either the condition (*e.g.* pain) or one or

more symptoms (*e.g.* pain) of the condition (*e.g.* sciatica), or to retard the progression of the condition (*e.g.* pain) or of one or more symptoms (*e.g.* pain) of the condition (*e.g.* sciatica), or to reduce the severity of the condition (*e.g.* pain) or of one or more symptoms (*e.g.* pain) of the condition (*e.g.* sciatica). In yet another embodiment, "treating" or "treatment" includes administering a compound described herein prophylactically.

[0063] As used herein, the terms "prophylactic agent" and "prophylactic agents" refer to any agent(s) which can be used in the prevention of a condition or one or more symptoms thereof and/or which prevents or impedes the onset, development, progression and/or severity of a condition. In some or any embodiments, the term "prophylactic agent" includes a compound provided herein. In some or any other embodiments, the term "prophylactic agent" does not refer a compound provided herein. In some or any embodiments, the agent is administered prophylactically, for example before surgery to prevent or impede the onset, duration, progression and/or severity of pain (*e.g.*, post surgical pain).

[0064] As used herein, the phrase "prophylactically effective amount" refers to the amount of a therapy (*e.g.*, prophylactic agent) which is sufficient to result in the prevention or reduction of the development, recurrence or onset of one or more symptoms associated with a condition, or to enhance or improve the prophylactic effect(s) of another therapy (*e.g.*, another prophylactic agent).

Compounds

[0065] Provided herein are compounds that can modulate the activity of voltage-gated ion channels (*e.g.*, voltage-gated sodium channels). The compounds can be formed as described herein and used for the treatment of conditions associated with voltage-gated sodium channel function. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain or a condition associated with pain. In some or any embodiments, the condition associated with voltage-gated sodium channel function is a condition associated with pain. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain, itch, cough, epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotrophic lateral sclerosis, glaucoma, ischemia, spasticity disorders and obsessive compulsive disorder. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain (in some embodiments, subacute or chronic pain). In some embodiments, the pain associated with voltage-gated sodium channel function includes pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal

injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, and pain associated with surgery (in some embodiments, ocular surgery).

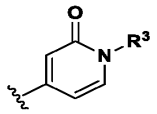
[0066] The aspects and embodiments described herein include the recited compounds as well as a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[0067] Included herein, if chemically possible, are all stereoisomers of the compounds, including diastereomers and enantiomers. Also included are mixtures of possible stereoisomers in any ratio, including, but not limited to, racemic mixtures. Unless stereochemistry is explicitly indicated in a structure at a particular atom, the structure is intended to embrace all possible stereoisomers of the compound depicted. If stereochemistry is explicitly indicated for one portion or portions of a molecule, but not for another portion or portions of a molecule, the structure is intended to embrace all possible stereoisomers for the portion or portions where stereochemistry is not explicitly indicated.

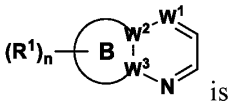
[0068] It will be apparent that certain structures recite specific stereochemistry at particular atoms.

[0069] Certain multicyclic structures provided herein are drawn with one or more floating substituents. Unless provided otherwise or otherwise clear from the context, the substituent(s) may be present on any atom of the multicyclic ring, where chemically feasible and valency rules permitting.

[0070] In some or any embodiments, provided herein is a compound of Formula (**I**), (**I-P2**), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

A is phenyl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, pyridinyl substituted with $\mathbf{R^3}$, thienyl substituted with $\mathbf{R^3}$, furanyl substituted with $\mathbf{R^3}$, pyrazolyl substituted with $\mathbf{R^3}$, indazolyl substituted with $\mathbf{R^3}$, benzoisothiazolyl substituted with $\mathbf{R^3}$, benzoisoxazolyl substituted with $\mathbf{R^3}$, unsubstituted pyrazolyl, pyrazolyl substituted with $\mathbf{R^3}$, or ;

$\mathbf{W^1}$ is -N= or -C(H)=;



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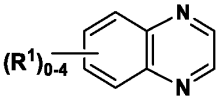

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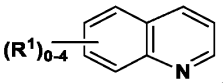

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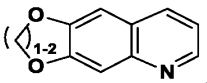

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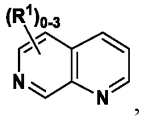

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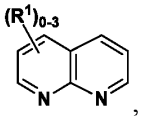

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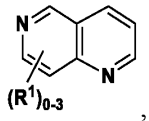

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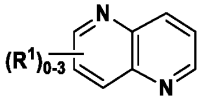

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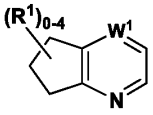

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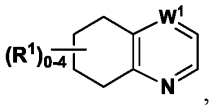

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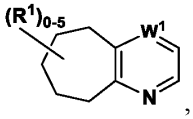

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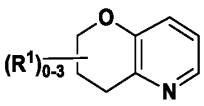

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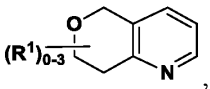

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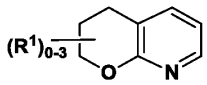
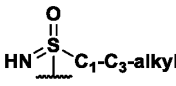


;

each **R**^{1} is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, or halogen;

each **R**^{2} is independently hydrogen, C_1-C_6 alkyl, or halo;

R^{3} is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxy-C_{1-3}alkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1-3}$alkyl, -$NHC(=NH)NH_2$, -$S(O)_2NH_2$, -$S(O)_2CH_3$, amino-C_1-C_3alkyl, halo-C_1-C_3alkyl, cyclopropyl, 4-membered heterocycloalkyl, or 

; where the cyclopropyl and the 4-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;**R**^{3a}, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 1 or 2;

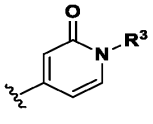
n is 0, 1, 2, or 4;

p is 0, 1, 2, or 3; and

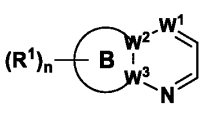
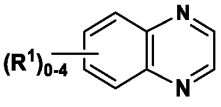
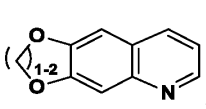
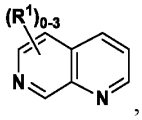
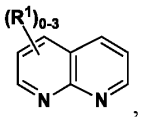
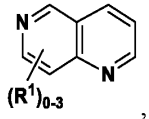
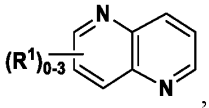
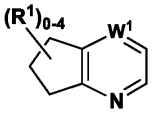
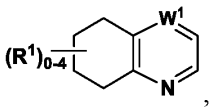
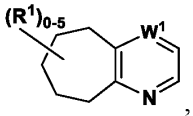
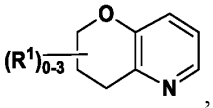
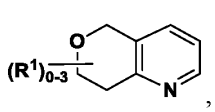
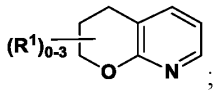
q is 0, 1, 2, or 3.

[0071] In some or any embodiments, provided herein is a compound of Formula (**I**), (**I-P2**), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

A is phenyl substituted with **R**^{3}, pyridinyl substituted with **R**^{3}, thienyl substituted with **R**^{3}, furanyl substituted with **R**^{3}, pyrazolyl substituted with **R**^{3}, indazolyl substituted with **R**^{3},

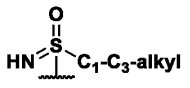
benzoisothiazolyl substituted with $\mathbf{R^3}$, benzoisoxazolyl substituted with $\mathbf{R^3}$, unsubstituted pyrazolyl, pyrazolyl substituted with $\mathbf{R^3}$, or ;

$\mathbf{W^1}$ is -N= or -C(H)=;

 is , , , , , , , , , , , or ;

each $\mathbf{R^1}$ is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, or halogen;

each $\mathbf{R^2}$ is independently hydrogen, C_1-C_6 alkyl, or halo;

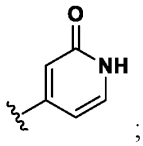
$\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(=NH)NH_2$, -$S(O)_2NH\mathbf{R}$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein $\mathbf{R}$ is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

$\mathbf{m}$ is 1 or 2;

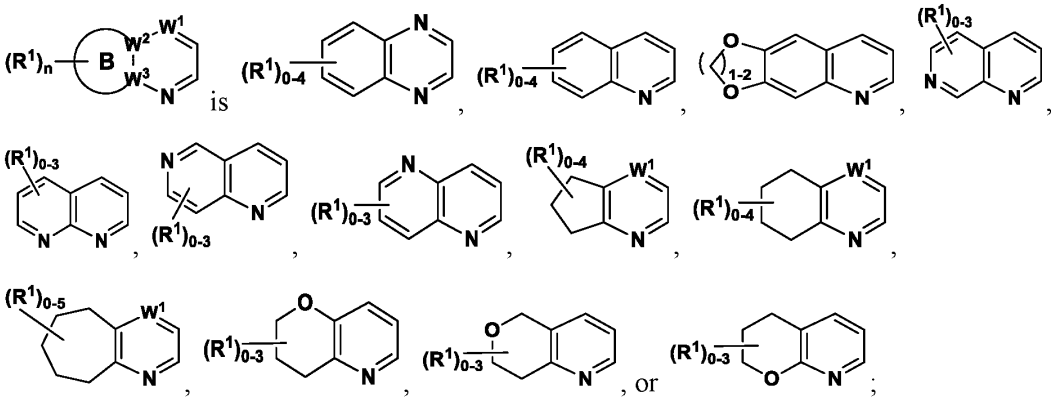
$\mathbf{n}$ is 0, 1, 2, or 4 and

$\mathbf{p}$ is 0, 1, 2, or 3.

[0072] In some or any embodiments, provided herein is a compound of Formula (**I**), (**I-P1**), (**I-P2**), or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein

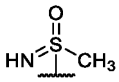
A is phenyl substituted with $\mathbf{R^3}$, pyridinyl substituted with $\mathbf{R^3}$, benzoisoxazolyl substituted with $\mathbf{R^3}$, unsubstituted pyrazolyl, pyrazolyl substituted with $\mathbf{R^3}$, or ;

$\mathbf{W^1}$ is -N= or -C(H)=;



each $\mathbf{R^1}$ is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, or halogen;

each $\mathbf{R^2}$ is independently hydrogen, C_1-C_6 alkyl, or halo;

$\mathbf{R^3}$ is -C(O)NH_2, -NH_2, -S(O)$_2NH_2$, -S(O)$_2CH_3$, or ;

m is 1 or 2;

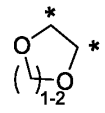
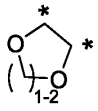
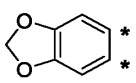
n is 0, 1, or 2; and

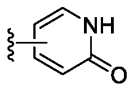
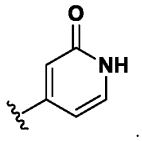
p is 0, 1, 2, or 3.

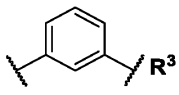
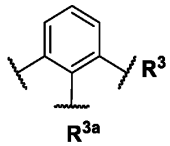
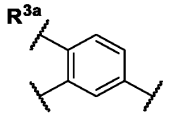
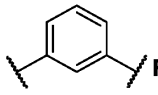
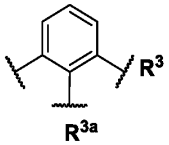
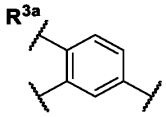
[0073] Embodiment 1: In some or any embodiments, provided herein is a compound of Formula (**I**), (**I-P1**), and (**I-P2**) wherein $\mathbf{R^1}$ is independently in each instance selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, halogen, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl. In some or any embodiments, $\mathbf{R^1}$ is independently in each instance selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, and halogen. In some or any embodiments, each $\mathbf{R^1}$ is hydrogen. In some or any embodiments, each $\mathbf{R^1}$ is C_1-C_6 alkyl. In some or any embodiments, each $\mathbf{R^1}$ is C_1-C_6 alkoxy. In some or any embodiments, each $\mathbf{R^1}$ is C_1-C_6 haloalkyl. In some or any embodiments, each $\mathbf{R^1}$ is halogen. In some or any embodiments, each $\mathbf{R^1}$ is C_3-C_6-cycloalkyl. In some or any embodiments, each $\mathbf{R^1}$ is C_3-C_6-cycloalkyl, C_1-C_3-alkyl.

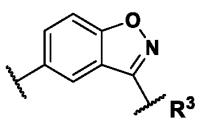
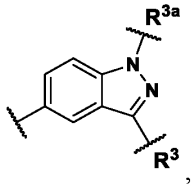
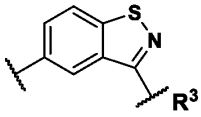
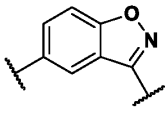
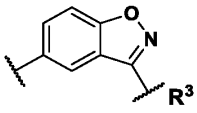
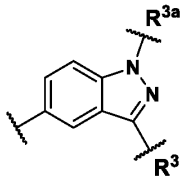
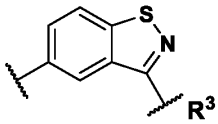
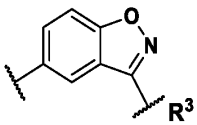
[0074] **Embodiment 1a:** In some or any embodiments, one $\mathbf{R^1}$ is present and is other than hydrogen. In some or any embodiments, two $\mathbf{R^1}$ are present and each is independently other than hydrogen. In some or any embodiments, three $\mathbf{R^1}$ are present and each is independently other than hydrogen. In some or any embodiments, at least one $\mathbf{R^1}$ is C_1-C_6 alkyl. In some or any embodiments, at least one $\mathbf{R^1}$ is $-CH_3$. In some or any embodiments, at least one $\mathbf{R^1}$ is C_1-C_6alkoxy. In some or any embodiments, at least one $\mathbf{R^1}$ is $-OCH_3$. In some or any embodiments, at least one $\mathbf{R^1}$ is C_1-C_6 haloalkyl. In some or any embodiments, at least one $\mathbf{R^1}$ is $-CF_3$. In some or any embodiments, at least one $\mathbf{R^1}$ is halo-C_1-C_6 alkoxy. In some or any embodiments, at least one $\mathbf{R^1}$ is $-OCF_3$. In some or any embodiments, at least one $\mathbf{R^1}$ is halogen. In some or any embodiments, at least one $\mathbf{R^1}$ is -Cl. In some or any embodiments, at least one $\mathbf{R^1}$ is -F. In some or any embodiments, $\mathbf{R^1}$ is C_3-C_6-cycloalkyl. In some or any embodiments, $\mathbf{R^1}$ is C_3-C_6-cycloalkylC_1-C_3-alkyl.

[0075] **Embodiment 1b:** In some or any embodiments, each $\mathbf{R^1}$ is independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy, and halogen. In some or any embodiments, each $\mathbf{R^1}$ is hydrogen.

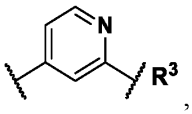
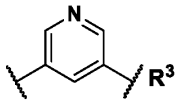
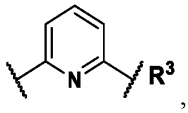
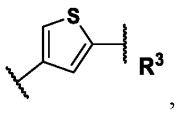
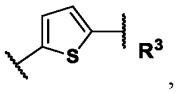
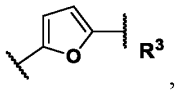
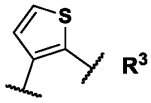
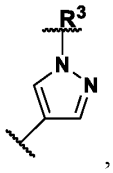
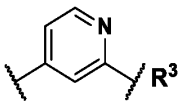
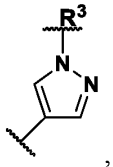
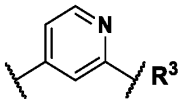
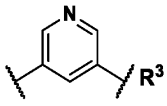
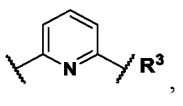
[0076] **Embodiment 1c:** In some or any embodiments, two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl. In some or any embodiments, two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and at least one of the remaining $\mathbf{R^1}$ is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl. In some or any embodiments,  is not .

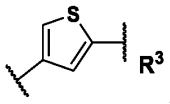
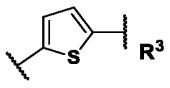
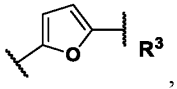
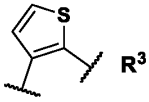
[0077] **Embodiment 2:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; or  optionally substituted with $(\mathbf{R^{3a}})_{q1}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is phenyl substituted with $\mathbf{R^3}$, pyridinyl substituted with $\mathbf{R^3}$, benzoisoxazolyl substituted with $\mathbf{R^3}$, unsubstituted pyrazolyl, pyrazolyl substituted with $\mathbf{R^3}$, or  .

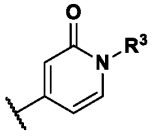
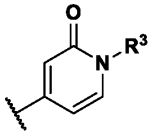
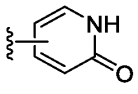
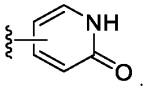
[0078] **Embodiment 2a:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is C_6-C_{10} aryl substituted with $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is phenyl substituted with $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  ,  , or  ,wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments including embodiments 1-1c, **A** is  , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  , wherein designates attachment to $\mathbf{R^3}$.

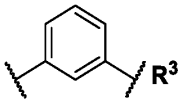
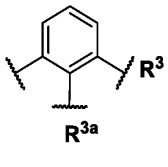
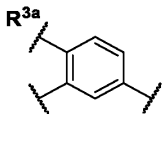
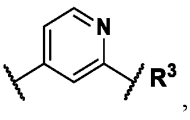
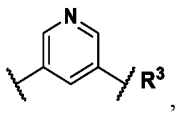
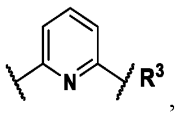
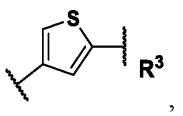
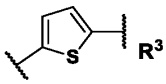
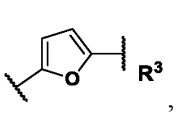
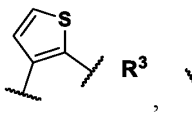
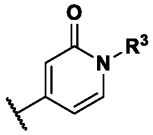
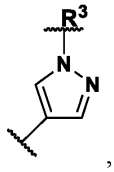
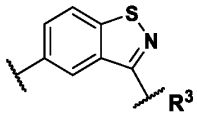
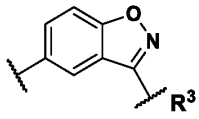
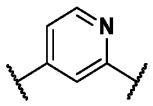
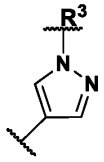
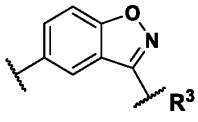
[0079] **Embodiment 2b:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 9- or 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 9-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , , , or , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein  designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein  designates attachment to $\mathbf{R^3}$. In some or any embodiments including embodiments 1-1c, **A** is , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of

Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$.

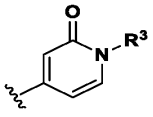
[0080] Embodiment 2c: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 5- or 6-membered heteroaryl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 5-membered heteroaryl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is 6-membered heteroaryl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is selected from the group consisting of: , , , , , , , and , wherein  designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is selected from the group consisting of:  and , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein designates attachment to $\mathbf{R^3}$. In some or any embodiments of Formula (**I**), (**I-P1**), (**I-P2**) including embodiments 1-1c, **A** is , wherein 

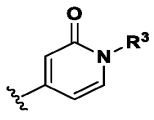
designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein  designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein  designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is , wherein  designates attachment to R^3.

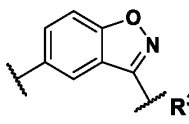
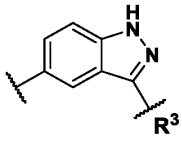
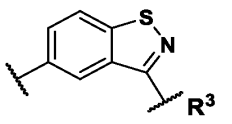
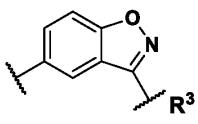
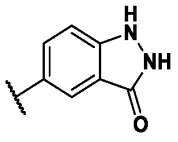
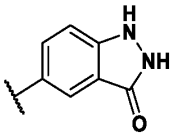
[0081] **Embodiment 2d:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  optionally substituted with $(R^{3a})_{q1}$. wherein  designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  wherein designates attachment to R^3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is  optionally substituted with $(R^{3a})_{q1}$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is .

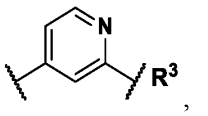
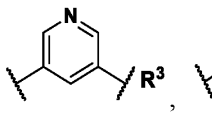
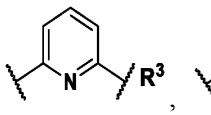
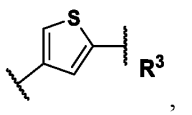
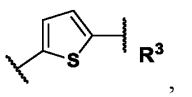
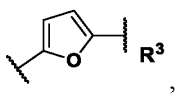
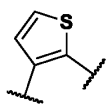
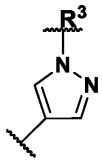
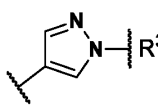
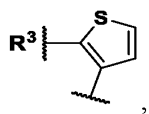
[0082] **Embodiment 2e**: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is selected from the group consisting of: , , , , , , , , , , , , , , , and , wherein designates attachment to **R**^{3}. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is selected from the group consisting of: , , and , wherein  designates attachment to **R**^{3}.

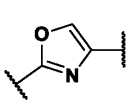
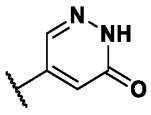
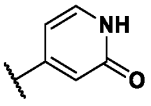
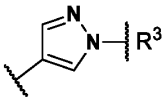
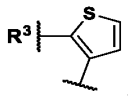
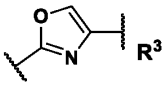
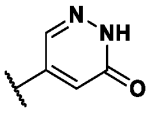
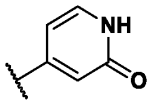
[0083] **Embodiment 2f:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is phenyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, pyridinyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, thienyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, furanyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, pyrazolyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, indazolyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, benzoisothiazolyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, benzoisoxazolyl substituted with **R**^{3} and optionally substituted with (**R**^{3a})$_q$, unsubstituted pyrazolyl, pyrazolyl substituted with **R**^{3}

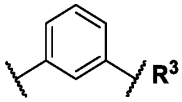
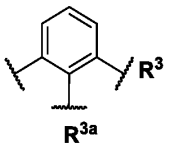
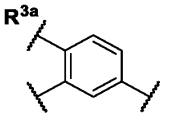
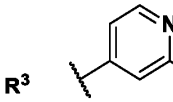
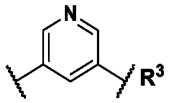
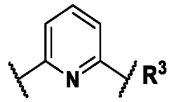
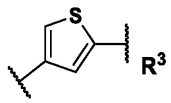
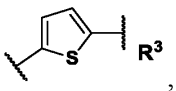
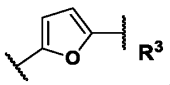
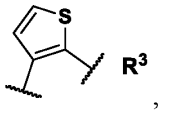
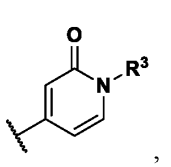
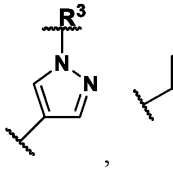
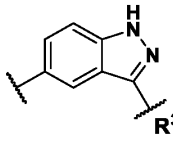
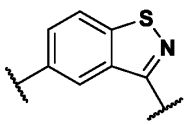
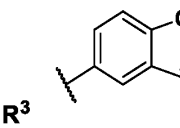
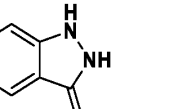
and optionally substituted with $(R^{3a})_q$, or  and optionally substituted with $(R^{3a})_q$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, the A ring is not further substituted with R^{3a}.

[0084] Embodiment 2g: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-1c, **A** is phenyl substituted with R^3, pyridinyl substituted with R^3, thienyl substituted with R^3, furanyl substituted with R^3, pyrazolyl substituted with R^3, indazolyl substituted with R^3, benzoisothiazolyl substituted with R^3, benzoisoxazolyl substituted with R^3, unsubstituted pyrazolyl, pyrazolyl substituted with R^3, or .

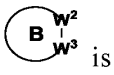
[0085] Embodiment 2h: In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is , , , , or . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is .

[0086] Embodiment 2j: In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is , , , , , , , , , .



, or . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is . In some or any embodiments of Formula (**I**) including embodiments 1-1c, **A** is .

[0087] **Embodiment 2k**: In some or any embodiments of formula (**I**) including embodiments 1-1c, **A** is selected from the group consisting of: , , , , , , , , , , , , , , , , , , , , , , and .

[0088] **Embodiment 3:** In some or any embodiments of formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-2d, $\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=. In some or any embodiments, $\mathbf{W^1}$ is -N= or -C(H)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -N=. In some or any embodiments including embodiments 1-2a, $\mathbf{W^1}$ is -C(H)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(halogen)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(cyclopropyl)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -N=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(H)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(halogen)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=. In some or any embodiments including embodiments 1-2d, $\mathbf{W^1}$ is -C(cyclopropyl)=.

[0089] **Embodiment 3a:** In some or any embodiments of Formula (**I**) and (**I-P2**) including embodiments 1-2g, $\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=. In some or any embodiments, $\mathbf{W^1}$ is -N= or -C(H)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -N=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(H)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(halogen)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(cyclopropyl)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -N=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(H)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(halogen)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^1}$ is -C(cyclopropyl)=. In some or any embodiments including embodiments 1-2g, $\mathbf{W^2}$ and $\mathbf{W_3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring.

[0090] **Embodiment 3b:** In some or any embodiments of Formula (**I**) including embodiments 1-2k, $\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C_1-C_6 alkoxy)=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, $\mathbf{W^1}$ is -N=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, $\mathbf{W^1}$

is -C(H)=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, W^1 is -C(halogen)=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, W^1 is -C(C_1-C_6 alkyl)=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, W^1 is -C(cyclopropyl)=. In some or any embodiments of Formula (**I**) including embodiments 1-2k, W^1 is -C(C_1-C_6 alkoxy)=.

[0091] **Embodiment 4:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 8-membered carbocyclic ring or a partially unsaturated 5 to 7-membered heterocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 8-membered carbocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered heterocyclic ring.

[0092] **Embodiment 4a:** In some or any embodiments of Formula (**I**) and (**I-P2**) including embodiments 1-3, W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an

additional N and where the remaining ring atoms are C. In some or any embodiments of Formula (**I**) and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered carbocyclic ring or a partially unsaturated 5 to 7-membered heterocyclic ring. In some or any embodiments of Formula (**I**) and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered carbocyclic ring. In some or any embodiments of Formula (**I**) and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered heterocyclic ring.

[0093] Embodiment 5: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring. In some or any embodiments including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is benzo ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered heterocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a 5 or 6-membered heteroaromatic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3

are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 8-membered carbocyclic ring or a partially unsaturated 5 to 7-membered heterocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 8-membered carbocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered heterocyclic ring.

[0094] Embodiment 5a: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a benzo ring or a 5 or 6-membered heteroaromatic ring; or one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C.

[0095] Embodiment 5b: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring. In some or any embodiments of Formula (**I**) and (**I-P1**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring. In some or any embodiments including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is benzo ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to

7-membered heterocyclic ring. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 and W^3 are each -C-; the dashed bond between W^2 and W^3 is a double bond, and  is a 5 or 6-membered heteroaromatic ring. In some or any embodiments of Formula (**I**) and (I-P1) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered carbocyclic ring or a partially unsaturated 5 to 7-membered heterocyclic ring. In some or any embodiments of Formula (**I**) and (**I-P1**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered carbocyclic ring. In some or any embodiments of Formula (**I**) and (**I-P1**) including embodiments 1-3, when W^2 and W^3 are each -C- and the dashed bond between W^2 and W^3 is a double bond, then  is not a partially unsaturated 5 to 7-membered heterocyclic ring.

[0096] Embodiment 6: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, one of W^2 and W^3 is -C- and the other is -N-; the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 is -C- and W^3 is -N-. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4, W^2 is -N- and W^3 is -C-. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4,  is a 5-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-4,  is a 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C.

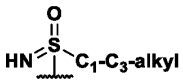
[0097] Embodiment 7: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or two R^2 are attached on adjacent carbons and together with the carbons to which

they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is hydrogen. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is halogen. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is C_1-C_6 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl.

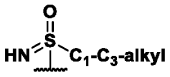
[0098] **Embodiment 7a:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, one $\mathbf{R^2}$ is present and is other than hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, two $\mathbf{R^2}$ are present and each is independently other than hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, three $\mathbf{R^2}$ are present and each is independently other than hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, at least one $\mathbf{R^2}$ is halogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, at least one $\mathbf{R^2}$ is -F. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, at least one $\mathbf{R^2}$ is C_1-C_6 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, at least one $\mathbf{R^2}$ is $-CH_3$.

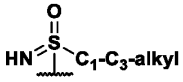
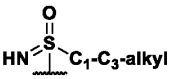
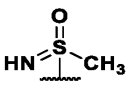
[0099] **Embodiment 7b:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, each $\mathbf{R^2}$ is independently selected from C_1-C_6 alkyl and halogen, wherein, in some embodiments, 1, 2, or 3 $\mathbf{R^2}$ are present, wherein, in some embodiments, 2 or 3 $\mathbf{R^2}$ are present. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-6, each $\mathbf{R^2}$ is hydrogen.

[00100] Embodiment 7c: In some or any embodiments of Formula (**I**) including embodiments 1-6, $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl, and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl, and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-6, $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is hydrogen. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is halogen. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is C_1-C_6 alkyl. In some or any embodiments including embodiments 1-6, $\mathbf{R^2}$ is halo-C_1-C_6 alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-6, two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl, and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-6, two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl, and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl.

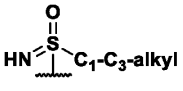
[00101] Embodiment 8: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -C(O)NH_2, -NH_2, -S(O)$_2$NH**R**, -S(O)$_2$$C_1$-$C_6$-alkyl, or 

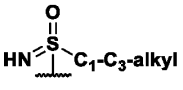
, wherein **R** is hydrogen, C_1-C_3 alkyl or C_3-C_5 cycloalkyl. In some or any embodiments including embodiments 1-7b, $\mathbf{R^3}$ is -C(O)NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$NH**R**. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including

embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$C$_1$-C$_6$-alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is hydrogen, C$_1$-C$_3$ alkyl or C$_3$-C$_5$ cycloalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is C$_1$-C$_3$ alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is C$_3$-C$_5$ cycloalkyl.

[00102] Embodiment 8a: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -C(O)NH$_2$, -NH$_2$, -S(O)$_2$NH**R**, -S(O)$_2$C$_1$-C$_6$-alkyl, or , wherein **R** is hydrogen, C$_1$-C$_3$ alkyl or C$_3$-C$_5$ cycloalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -C(O)NH$_2$. In some or any embodiments including embodiments 1-7b, $\mathbf{R^3}$ is -NH$_2$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$NH**R**. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$C$_1$-C$_6$-alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is hydrogen, C$_1$-C$_3$ alkyl or C$_3$-C$_5$ cycloalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is C$_1$-C$_3$ alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, **R** is C$_3$-C$_5$ cycloalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$NH$_2$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -S(O)$_2$CH$_3$. In some or any embodiments including embodiments 1-7b, $\mathbf{R^3}$ is .

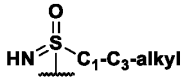
[00103] Embodiment 8b: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is hydrogen, -OH, -B(OH)$_2$, -COOH,

hydroxyalkyl, -C(=NH)NH_2, -C(O)NH_2, -NH_2, -NHC(O)C_{1-3}alkyl, -NHC(=NH)NH_2, -$S(O)_2NHR$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

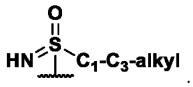
, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6 cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is halo. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -OH. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -$B(OH)_2$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -COOH. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is hydroxyalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -C(=NH)NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -C(O)NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -NH_2. In some or any embodiments o of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -NHC(O)C_{1-3}alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -NHC(=NH)NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -$S(O)_2NHR$. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is -$S(O)_2C_1$-C_6-alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is amino-C_1-C_6alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is halo-C_1-C_3alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is C_3-C_6-cycloalkyl substituted with one -NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is 3- to 6-membered heterocycloalkyl substituted with one -NH_2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b, $\mathbf{R^3}$ is 

. In some

or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-7b and 8b, R^3 is other than hydrogen.

[00104] Embodiment 8c: In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is hydrogen, -OH, $-B(OH)_2$, -COOH, hydroxyalkyl, $-C(=NH)NH_2$, $-C(O)NH_2$, $-NH_2$, $-NHC(O)C_{1\text{-}3}$alkyl, $-NHC(O)NH_2$, $-NHS(O)_2NH_2$, $-NHC(=NH)NH_2$, $-S(O)_2NHR$, $-S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5cycloalkyl; where the C_3-C_6cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one $-NH_2$; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is hydrogen. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is -OH. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-B(OH)_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is -COOH. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is hydroxyalkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-C(=NH)NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-C(O)NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-NHC(O)C_{1\text{-}3}$alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-NHC(O)NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-NHS(O)_2NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-NHC(=NH)NH_2$. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-S(O)_2NHR$, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5cycloalkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is $-S(O)_2C_1$-C_6-alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is amino-C_1-C_6alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is halo-C_1-C_3alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is C_3-C_6-cycloalkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3 is 3- to 6-membered heterocycloalkyl. In some or any embodiments of Formula (**I**) including embodiments 1-7c, R^3

is . In some or any embodiments of Formula (**I**) including embodiments 1-7c, $\mathbf{R^3}$ is 3- to 6-membered heterocycloalkyl optionally substituted with one -NH_2. In some or any embodiments of Formula (**I**) including embodiments 1-7c, $\mathbf{R^3}$ is 3- to 6-membered heterocycloalkyl substituted with one -NH_2. In some or any embodiments of Formula (**I**) including embodiments 1-7c, $\mathbf{R^3}$ is amino-C_1-C_6alkyl, wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo. In some or any embodiments of Formula (**I**) including embodiments 1-7c, $\mathbf{R^3}$ is amino-C_1-C_6alkyl, wherein the alkyl in amino-C_1-C_6alkyl is further substituted with 1, 2, 3, or 4 halo. In one or more embodiments including embodiments 1-7c, **R3** is amino-C_1-C_3alkyl. In one or more embodiments including embodiments 1-7c, $\mathbf{R^3}$ is amino-C_1-C_3alkyl, wherein the alkyl in amino-C_1-C_3alkyl is further substituted with 1, 2, 3, or 4 halo.

[00105] Embodiment 9: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, $\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl. In some or any embodiments including embodiments 1-8b, $\mathbf{R^{3a}}$ is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, each $\mathbf{R^{3a}}$ is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, one $\mathbf{R^{3a}}$ is hydrogen and the other $\mathbf{R^{3a}}$ is other than hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, at least one $\mathbf{R^{3a}}$ is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, $\mathbf{R^{3a}}$ is halogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, $\mathbf{R^{3a}}$ is C_1-C_3 alkyl. In some or any embodiments including embodiments 1-8b, $\mathbf{R^{3a}}$ is C_3-C_6 cycloalkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, one $\mathbf{R^{3a}}$ is halogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, one $\mathbf{R^{3a}}$ is C_1-C_3 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-8b, one $\mathbf{R^{3a}}$ is C_3-C_6 cycloalkyl.

[00106] Embodiment 9a: In some or any embodiments of Formula (**I**) including embodiments 1-8c, $\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl. In some or any embodiments including embodiments 1-8c, $\mathbf{R^{3a}}$ is hydrogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, each $\mathbf{R^{3a}}$ is hydrogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, one $\mathbf{R^{3a}}$

is hydrogen and the other R^{3a} is other than hydrogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, at least one R^{3a} is hydrogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, R^{3a} is halogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, R^{3a} is C_1-C_3 alkyl. In some or any embodiments including embodiments 1-8c, R^{3a} is C_3-C_6 cycloalkyl. In some or any embodiments of Formula (**I**) including embodiments 1-8c, one R^{3a} is halogen. In some or any embodiments of Formula (**I**) including embodiments 1-8c, one R^{3a} is C_1-C_3 alkyl. In some or any embodiments of Formula (**I**) including embodiments 1-8c, one R^{3a} is C_3-C_6 cycloalkyl.

[00107] Embodiment 10: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-9a, **m** is 0, 1, 2, or 3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-9a, **m** is 1 or 2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-9a, **m** is 0. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-9a, **m** is 1. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-9a, **m** is 2. In some or any embodiments, **m** is 3.

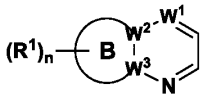
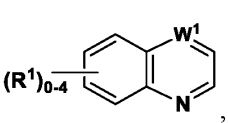
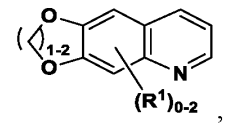
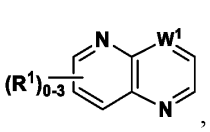
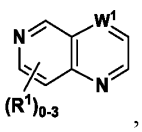
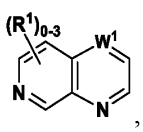
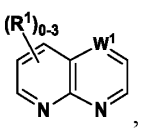
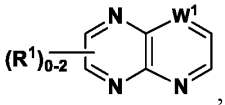
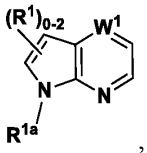
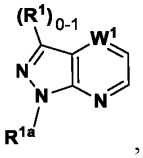
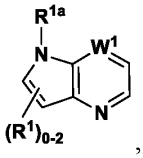
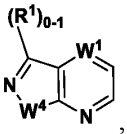
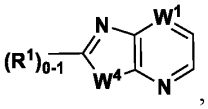
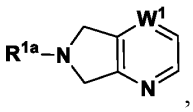
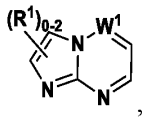
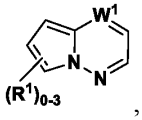
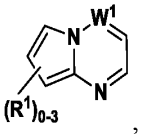
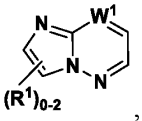
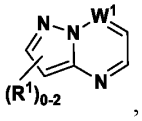
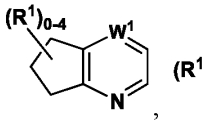
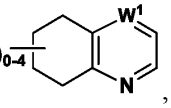
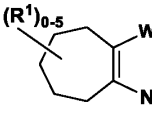
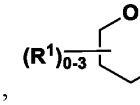
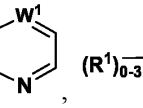
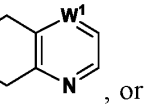
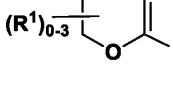
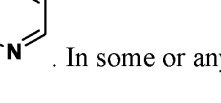
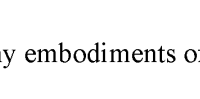
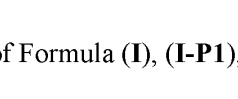
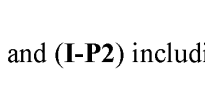
[00108] Embodiment 11: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 0, 1, 2, 3, or 4. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 0, 1, or 2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 0. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 1. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-10, **n** is 3. In some or any embodiments including embodiments 1-10, **n** is 4.

[00109] Embodiment 12: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 0, 1, 2, 3, 4, 5, or 6. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 0, 1, 2, or 3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 0. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 1. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 2. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 4. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**)

including embodiments 1-11, **p** is 5. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-11, **p** is 6.

[00110] Embodiment 13: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-12, **q** is 0, 1, 2, or 3. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-12, **q** is 0. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-12, **q** is 1. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-12, **q** is 2. In some or any embodiments including embodiments 1-12, **q** is 3.

[00111] Embodiment 14: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-12, **q1** is 0, 1, or 2. In some or any embodiments including embodiments 1-12, **q1** is 0. In some or any embodiments including embodiments 1-12, **q1** is 1. In some or any embodiments including embodiments 1-12, **q1** is 2.

[00112] Embodiment 15: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , 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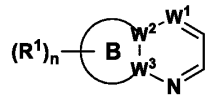
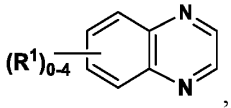
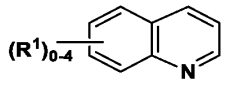
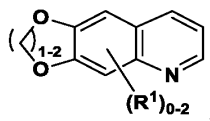
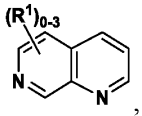
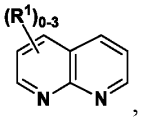
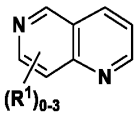
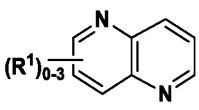
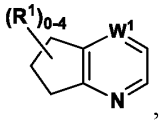
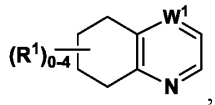
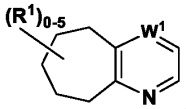
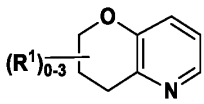
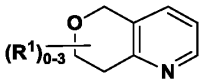
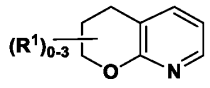
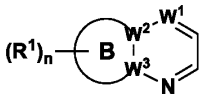
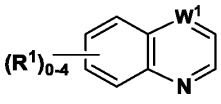
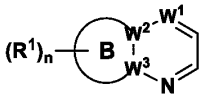
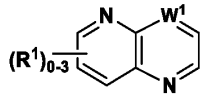
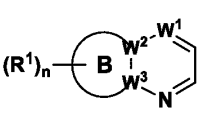
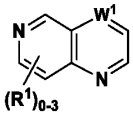
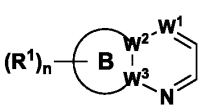
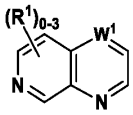
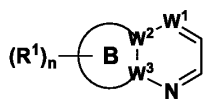
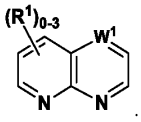
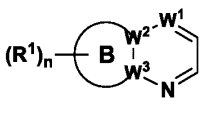
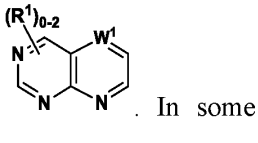
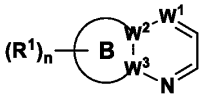
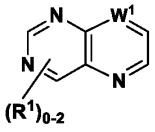
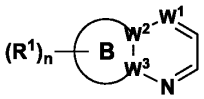
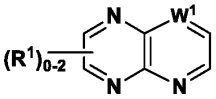
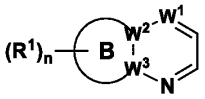
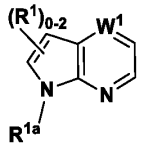
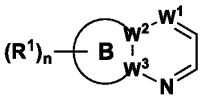
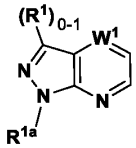
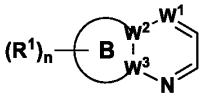
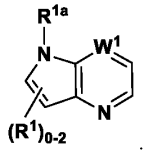
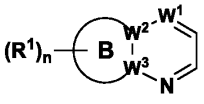
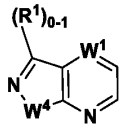
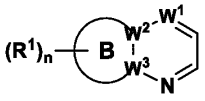
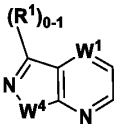
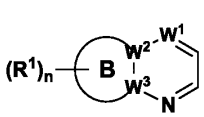
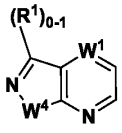
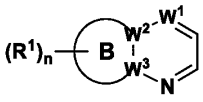
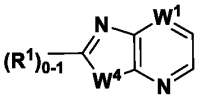
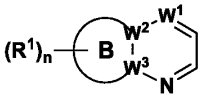
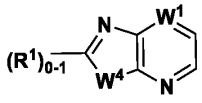
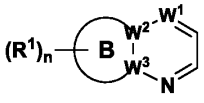
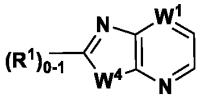
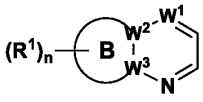
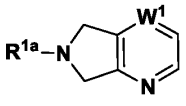
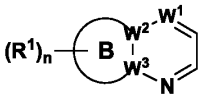
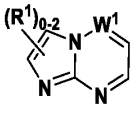
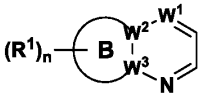
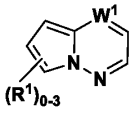
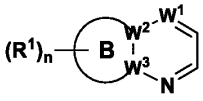
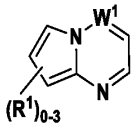
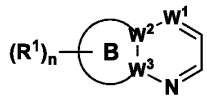
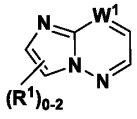
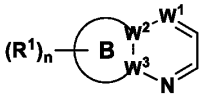
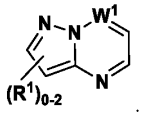
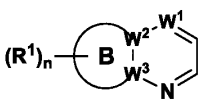
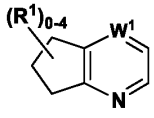
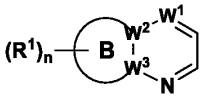
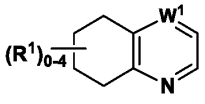
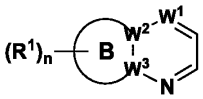
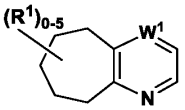
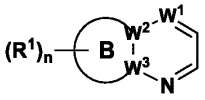
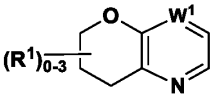
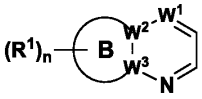
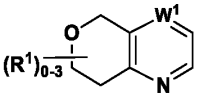
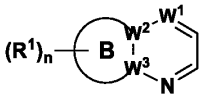
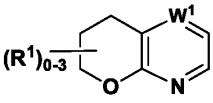
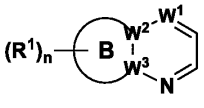
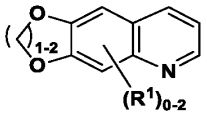
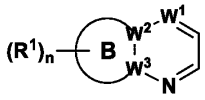
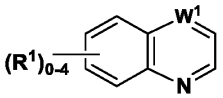
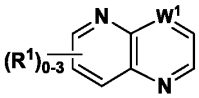
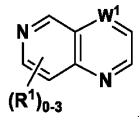
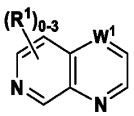
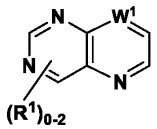
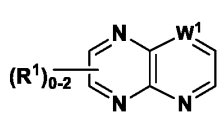
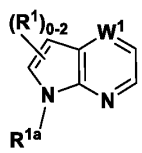
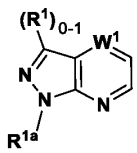
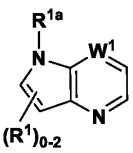
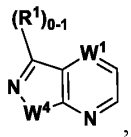
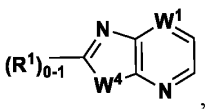
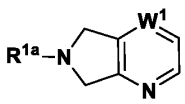
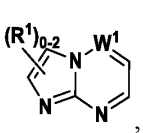
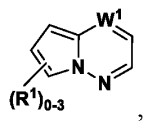
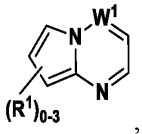
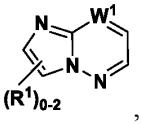
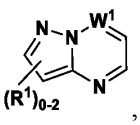
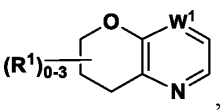
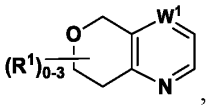
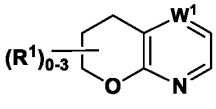
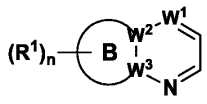
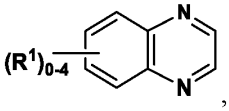
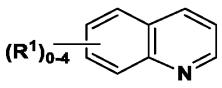
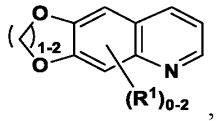
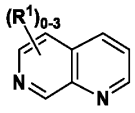
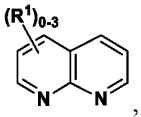
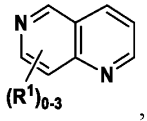
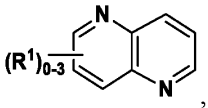
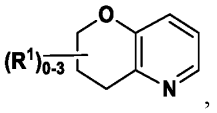
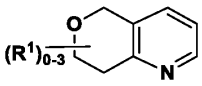
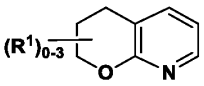
embodiments 1-14,  is , , , , , , , , , , , , or . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,

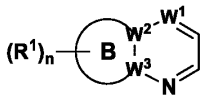
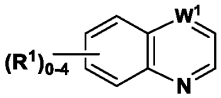
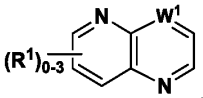
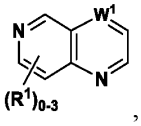
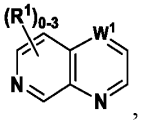
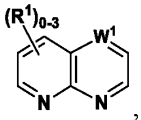
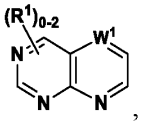
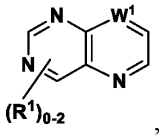
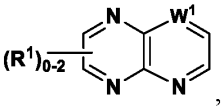
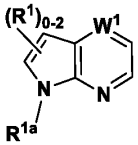
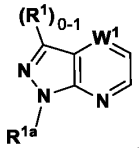
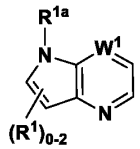
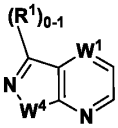
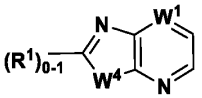
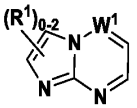
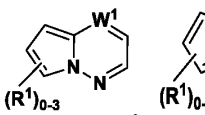
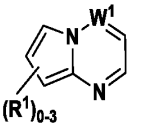
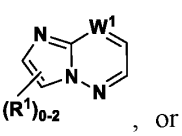
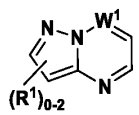
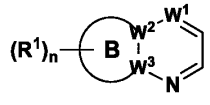
 is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is ; in some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is  and **W**^{4} is O; and in some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is  and **W**^{4} is S. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,

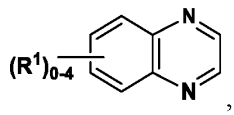
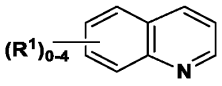
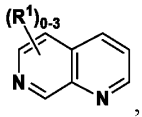
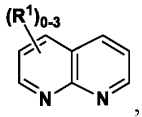
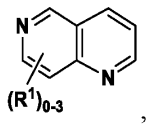
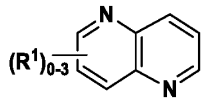
 is ; in some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is  and W^4 is O; and in some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is  and W^4 is S. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and

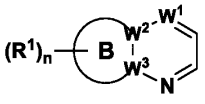
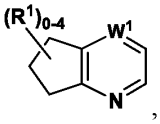
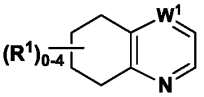
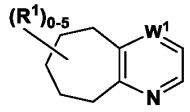
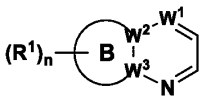
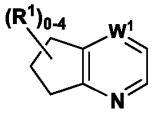
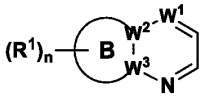
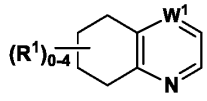
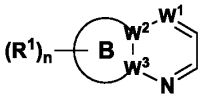
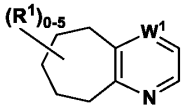
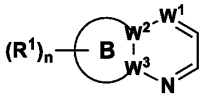
(**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is .

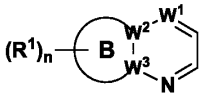
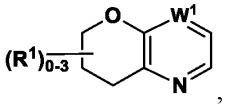
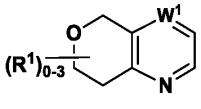
[00113] Embodiment 15a: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , , , , , , , , , , , , ,

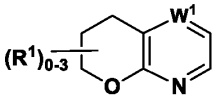
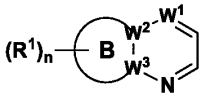
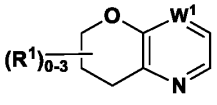
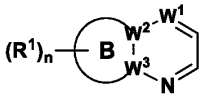
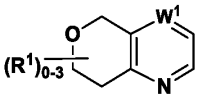
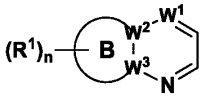
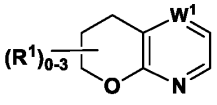
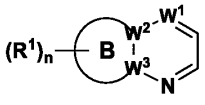
, , , , , , , or . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , , , , , , , , or .

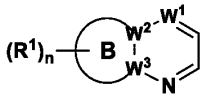
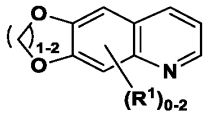
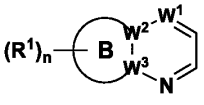
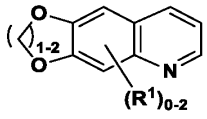
[00114] Embodiment 15b: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , , , , , , , , , , , , , , , , or . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is

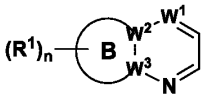
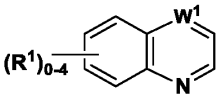
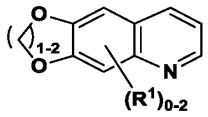
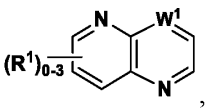
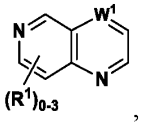
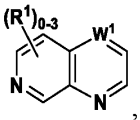
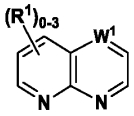
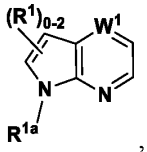
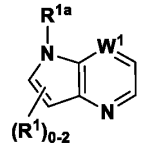







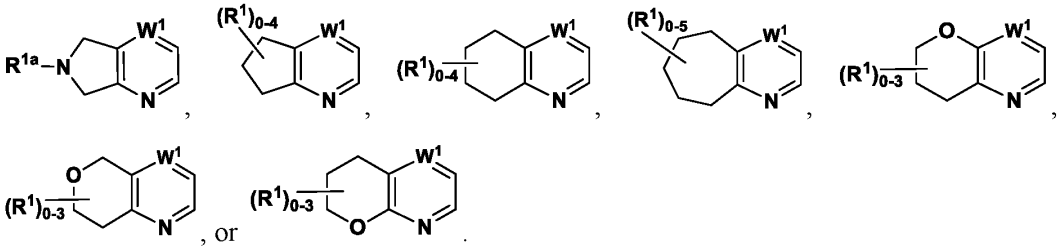
[00115] **Embodiment 15c:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , or . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is not one of the ring systems recited in this paragraph.

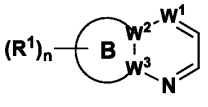
[00116] **Embodiment 15d:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , or

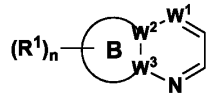

. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is not one of the ring systems recited in this paragraph.

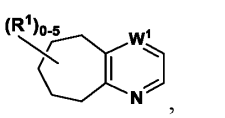
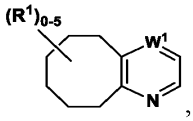
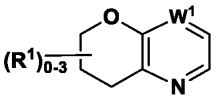
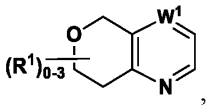
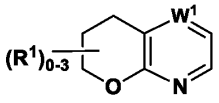
[00117] Embodiment 15e: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is . In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is not .

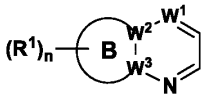
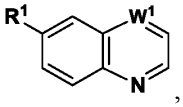
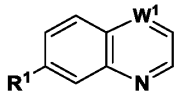
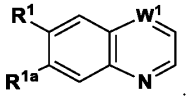
[00118] Embodiment 16: In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-14,  is , , , , , , , ,



[00119] **Embodiment 16a:** In some or any embodiments of Formula (**I**) including embodiments 1-14,  is

[00120] **Embodiment 16b:** In some or any embodiments of Formula (**I**) including embodiments 1-14,  is

, , ,  or .

[00121] **Embodiment 16c:** In some or any embodiments of Formula (**I**) and (**I-P1**) including embodiments 1-14,  is , , or .

[00122] **Embodiment 17:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-16a, $\mathbf{R^{1a}}$ is hydrogen. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-16a, $\mathbf{R^{1a}}$ is C_1-C_6 alkyl. In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**) including embodiments 1-16a, $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkyl. In some or any embodiments, $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkylC_1-C_3-alkyl.

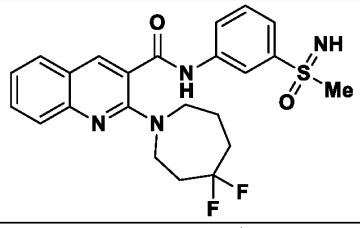
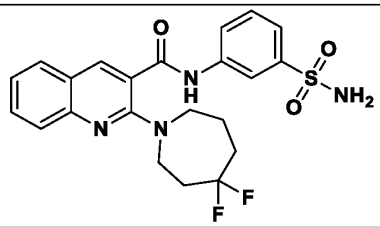
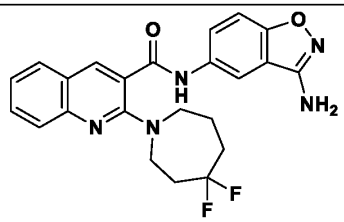
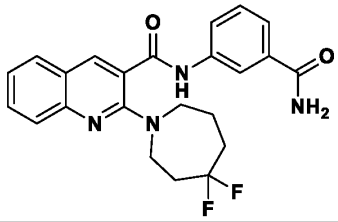
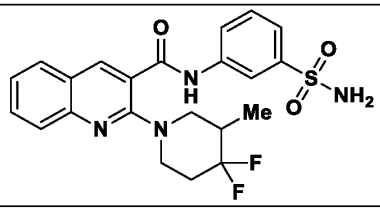
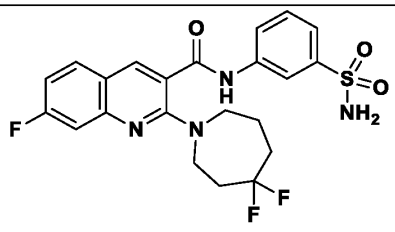
[00123] **Embodiment 17a:** In some or any embodiments of Formula (**I**) including embodiments 1-16a, $\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl. In some or any embodiments of Formula (**I**), including embodiments 1-16a, $\mathbf{R^{1a}}$ is halogen.

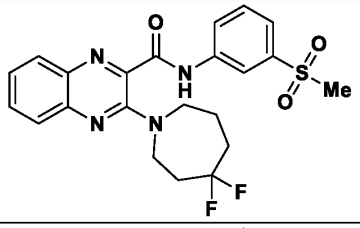
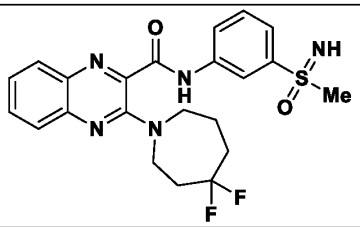
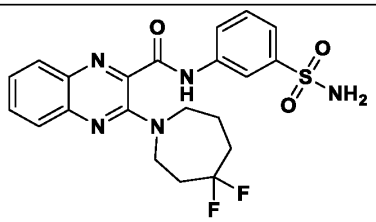
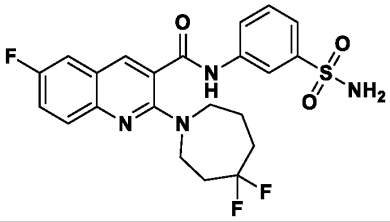
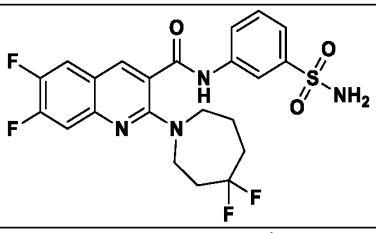
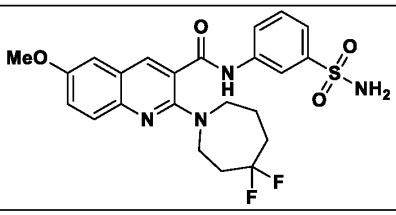
[00124] **Embodiment 18:** In some or any embodiments of Formula (**I**), (**I-P1**), and (**I-P2**), the compound is selected from any of compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A.

[00125] **Embodiment 18a:** In some or any embodiments of Formula (**I**) and (**I-P2**), the compound is selected from any of compounds 1-127 and 169-206, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A.

[00126] **Embodiment 18c:** In some or any embodiments of Formula (**I**), the compound is selected from any of compounds 1-206, or a pharmaceutically acceptable salt and/or an isomer thereof, from Table A.

Table A

Cmpd No.	Structure
1	
2	
3	
4	
5	
6	

Cmpd No.	Structure
7	
8	
9	
10	
11	
12	

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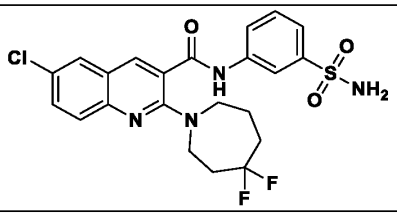
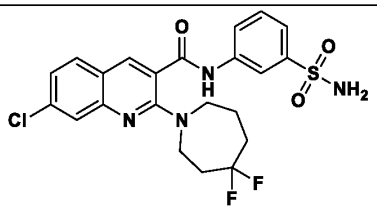
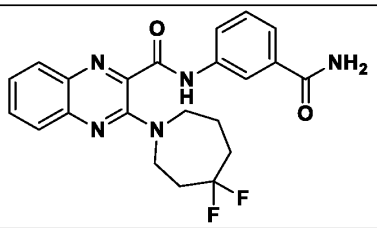
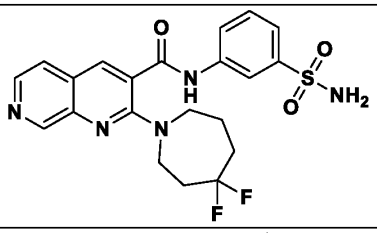
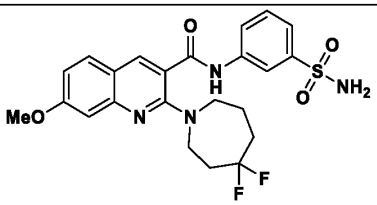
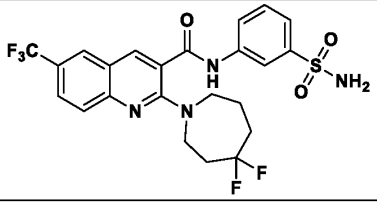
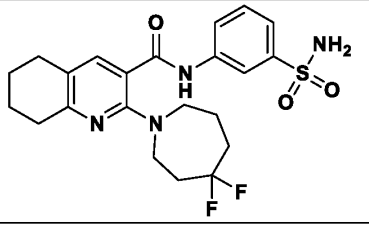
13	
14	
15	
16	
17	
18	
19	

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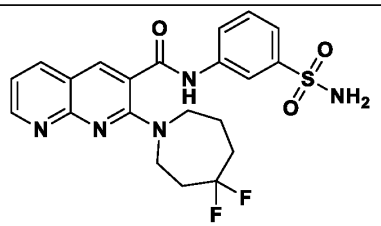
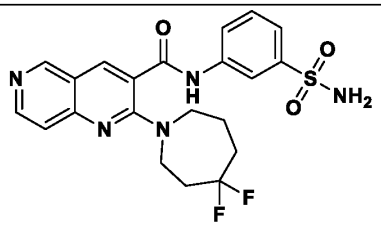
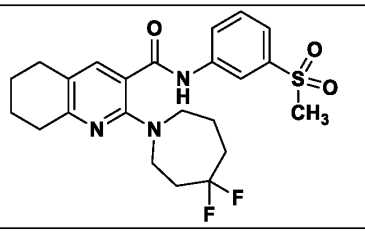
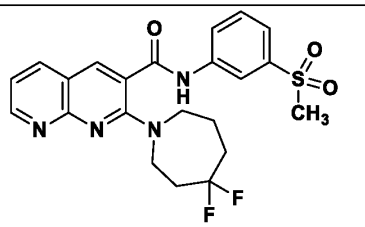
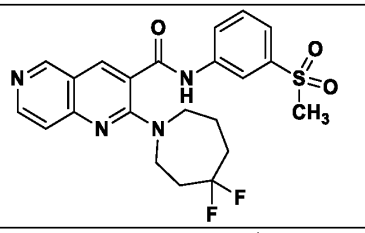
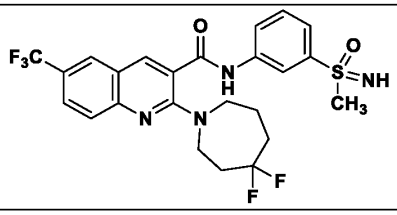
20	
21	
22	
23	
24	
25	

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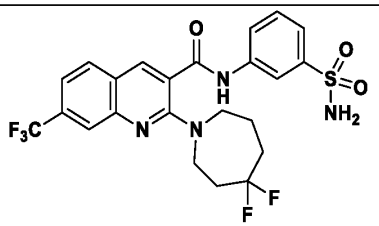
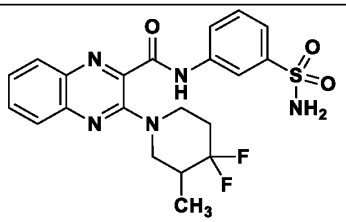
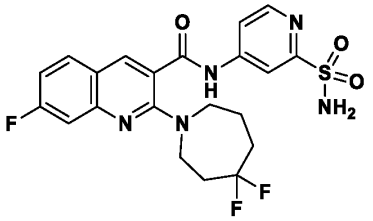
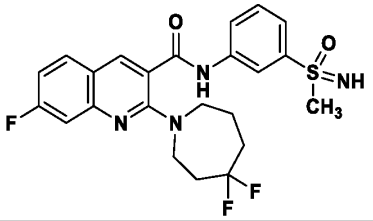
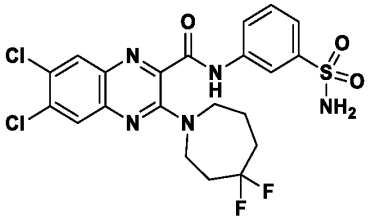
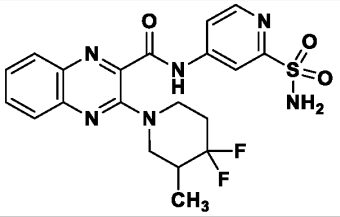
26	
27	
28	
29	
30	
31	

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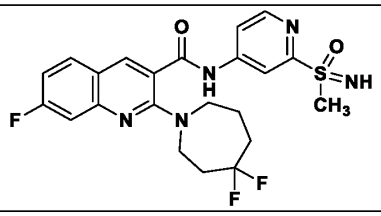
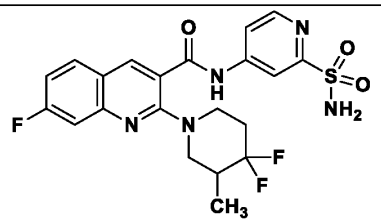
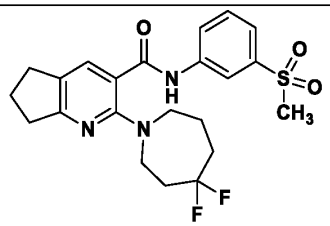
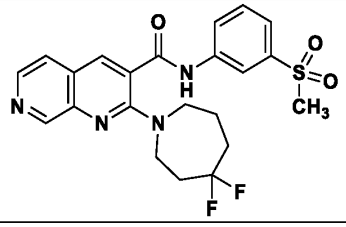
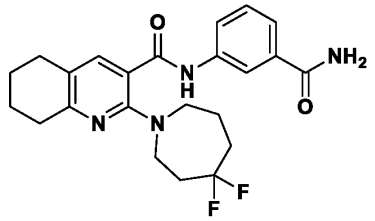
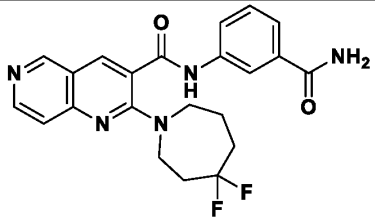
32	
33	
34	
35	
36	
37	

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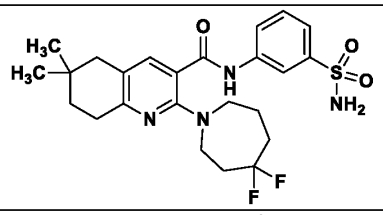
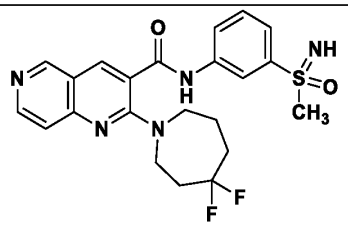
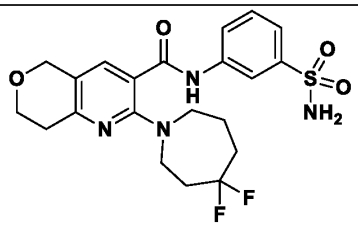
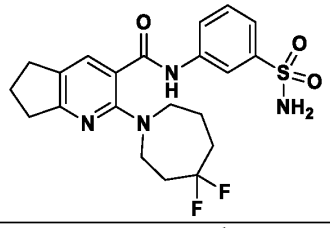
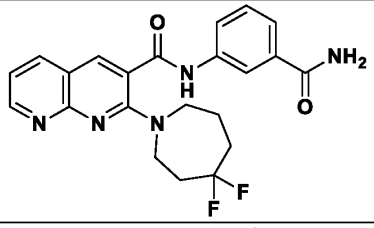
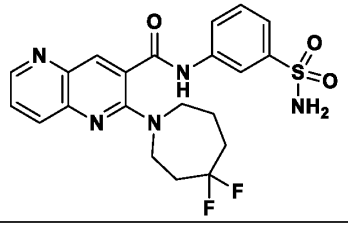
38	
39	
40	
41	
42	
43	

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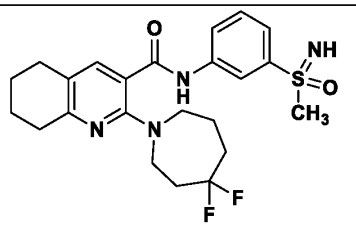
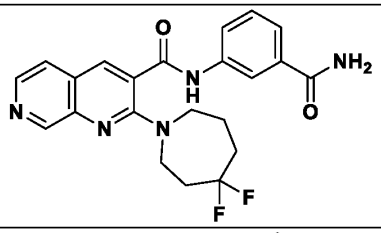
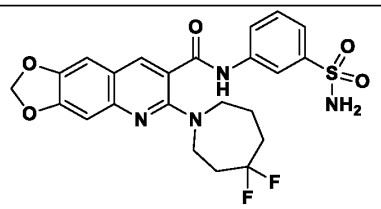
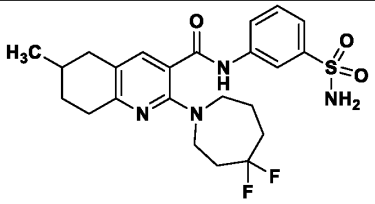
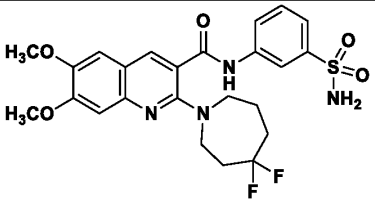
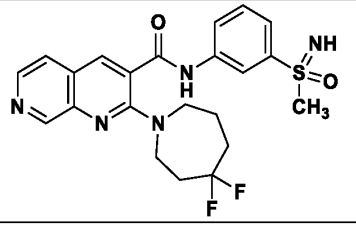
44	
45	
46	
47	
48	
49	

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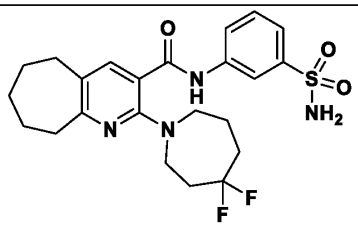
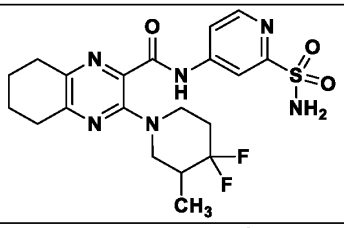
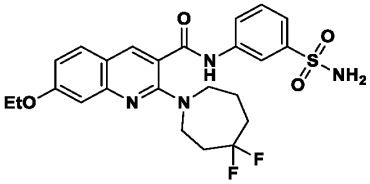
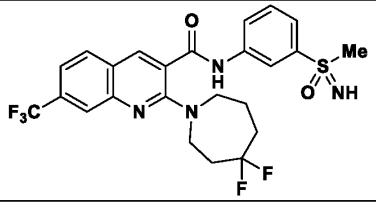
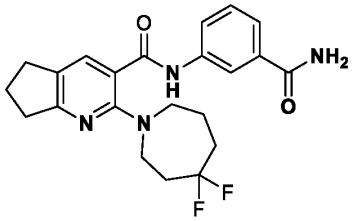
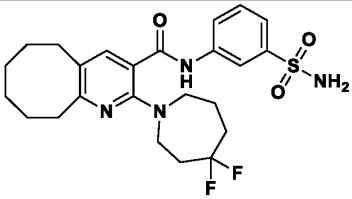
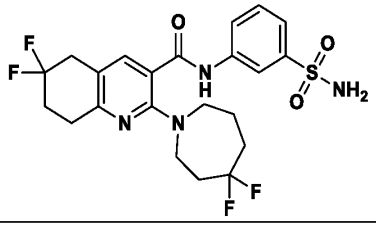
50	
51	
52	
53	
54	
55	
56	

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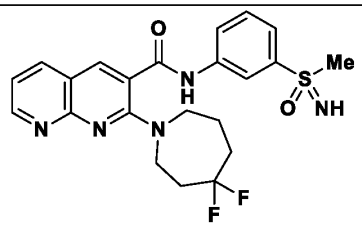
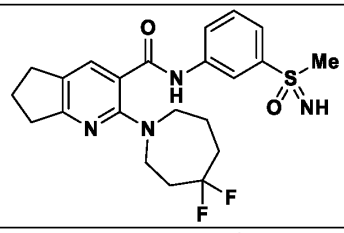
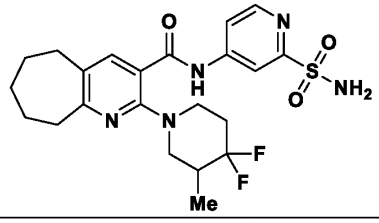
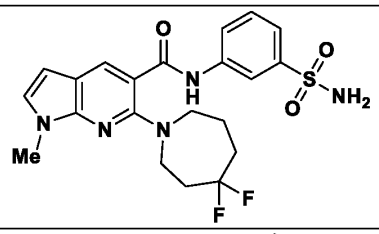
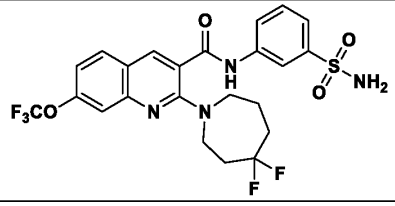
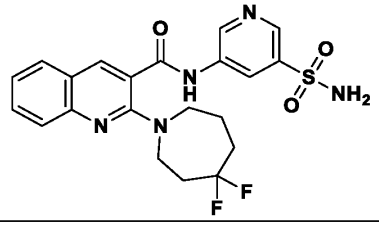
57	
58	
59	
60	
61	
62	

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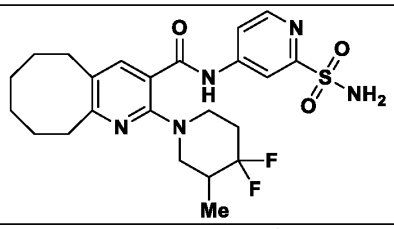
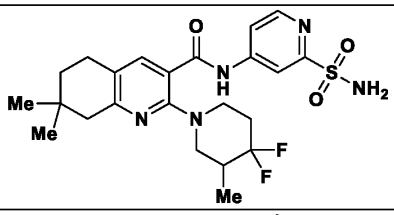
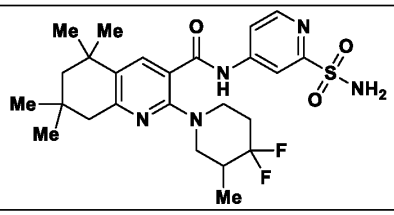
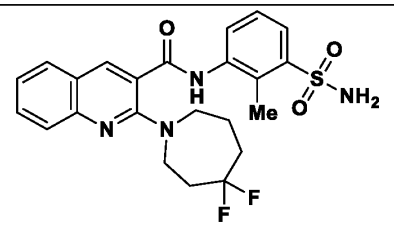
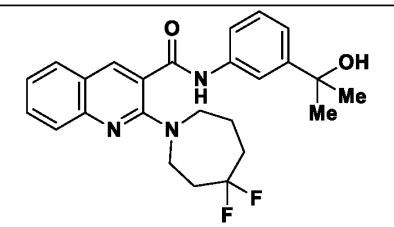
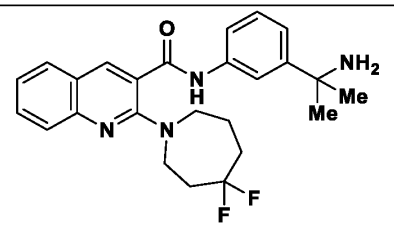
63	
64	
65	
66	
67	
68	

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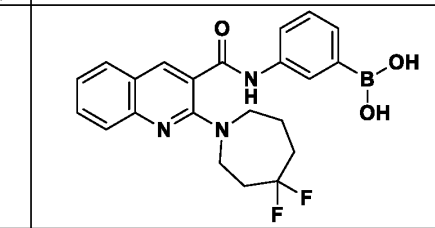
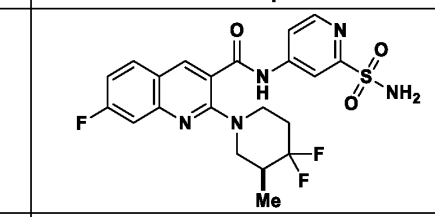
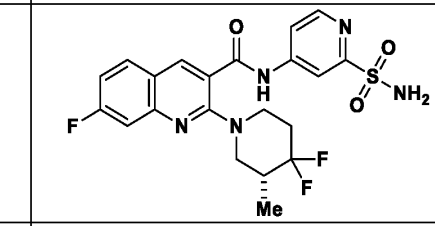
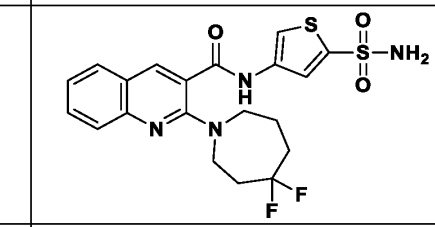
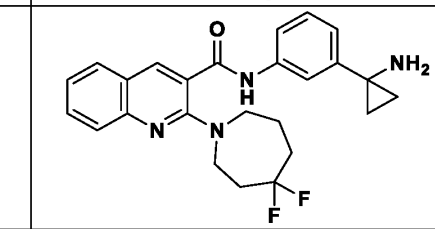
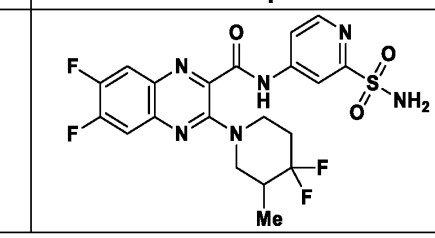
69	
70	
71	
72	
73	
74	

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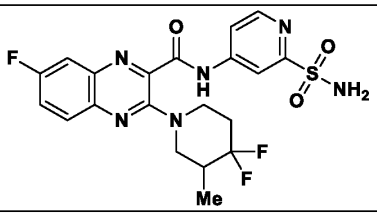
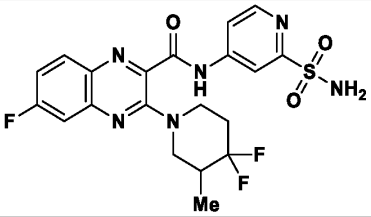
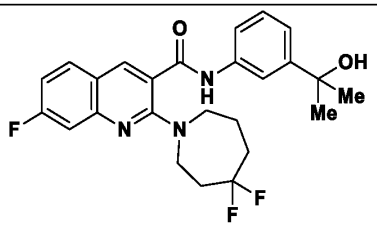
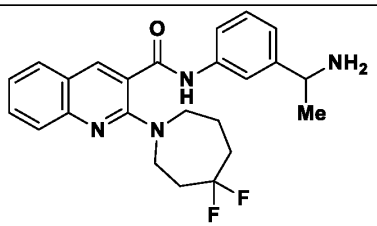
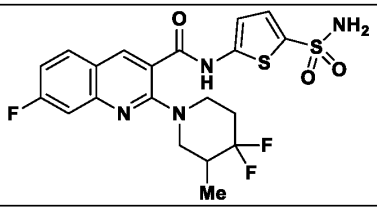
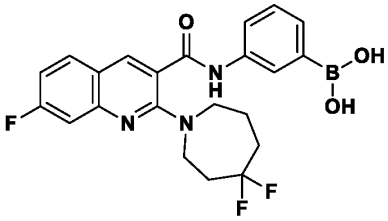
75	
76	
77	
78	
79	
80	

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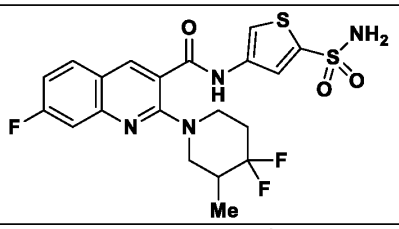
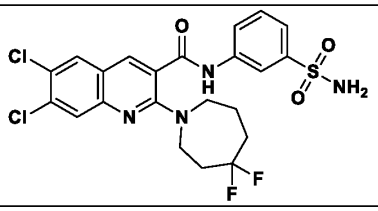
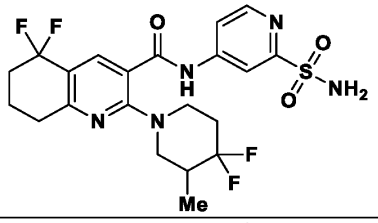
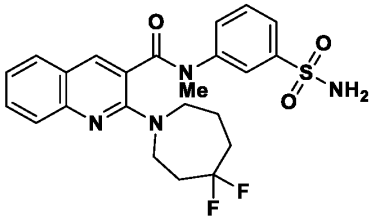
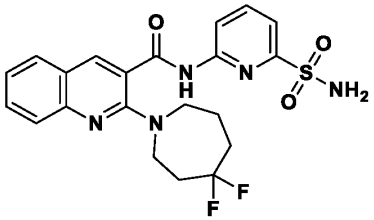
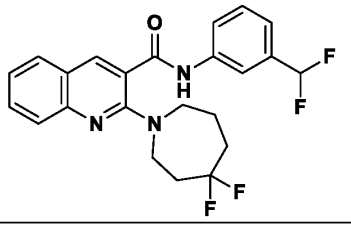
81	
82	
83	
84	
85	
86	

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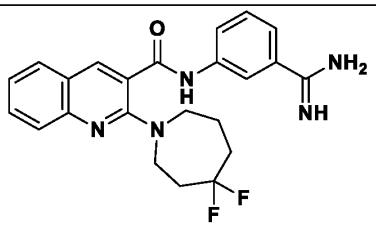
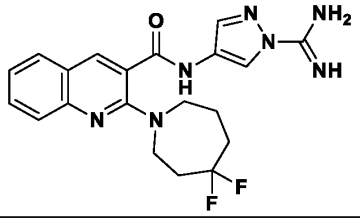
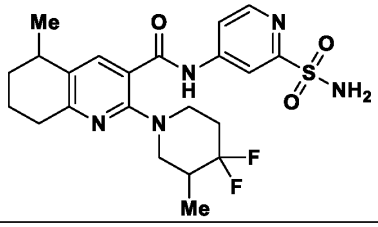
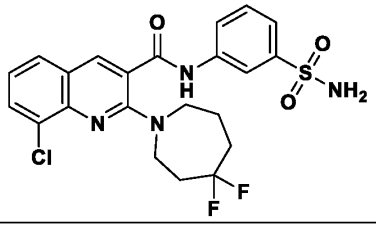
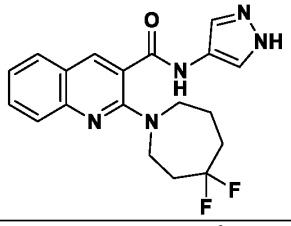
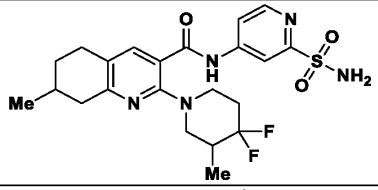
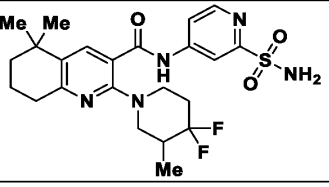
87	
88	
89	
90	
91	
92	
93	

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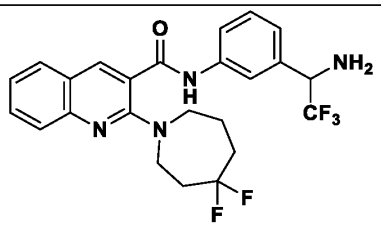
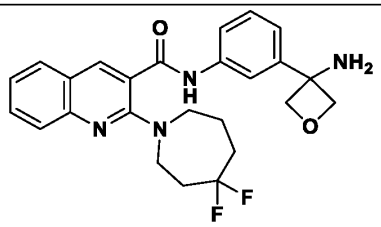
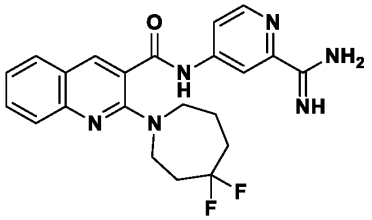
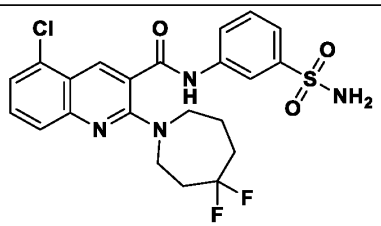
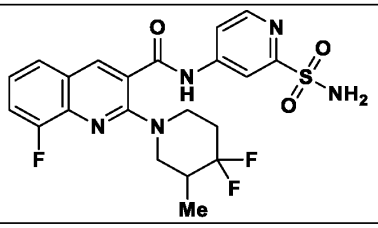
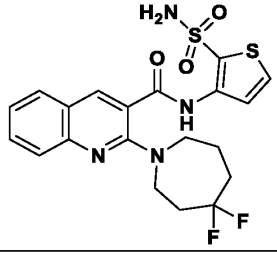
94	
95	
96	
97	
98	
99	

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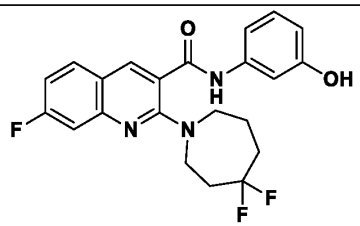
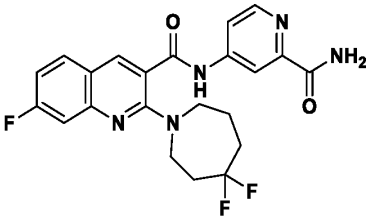
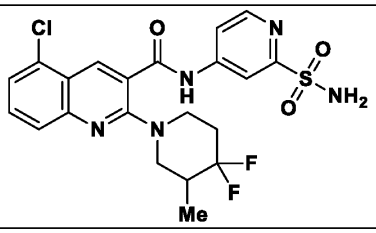
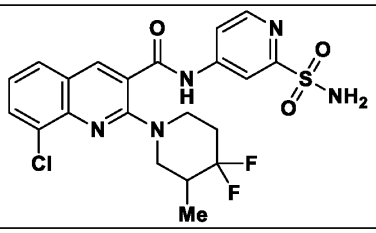
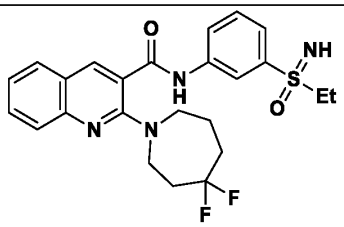
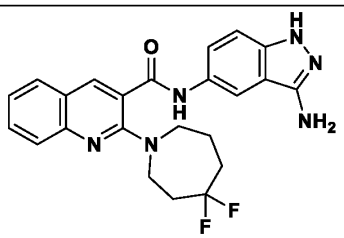
100	
101	
102	
103	
104	
105	

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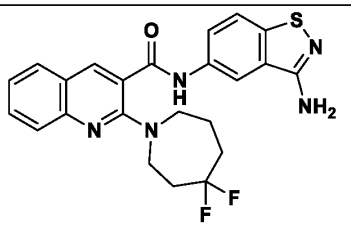
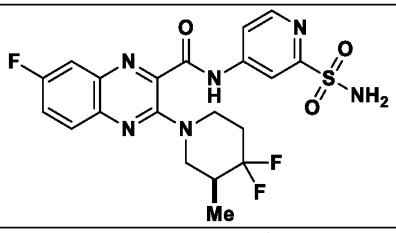
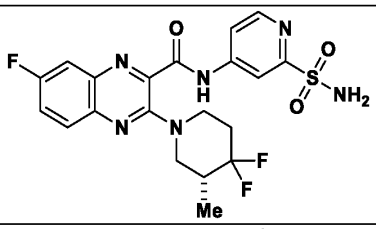
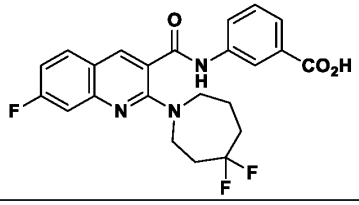
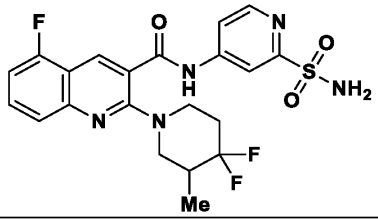
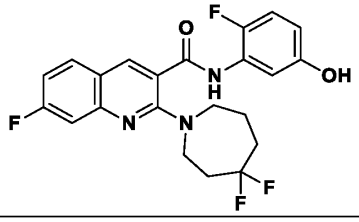
106	
107	
108	
109	
110	
111	

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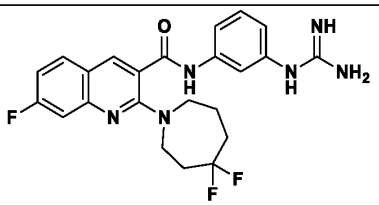
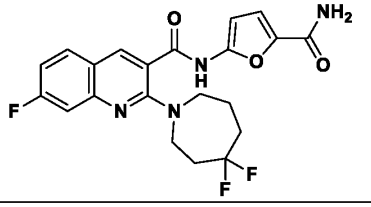
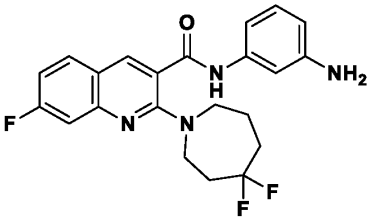
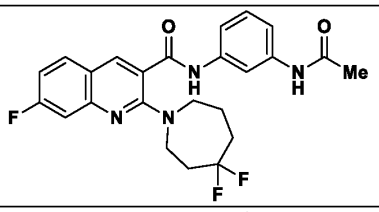
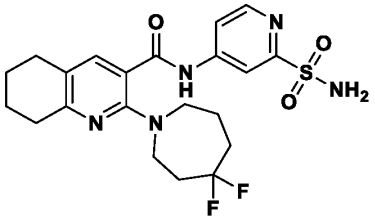
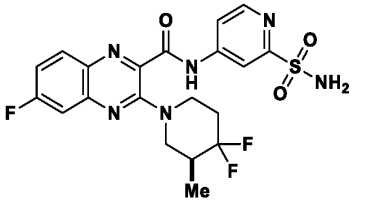
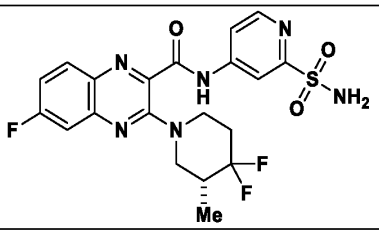
112	
113	
114	
115	
116	
117	
118	

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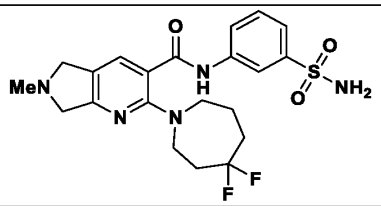
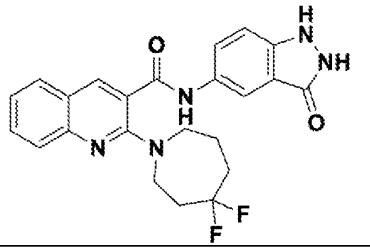
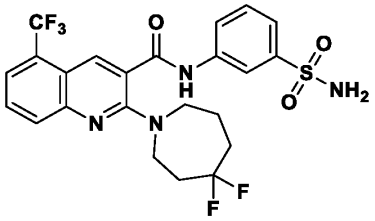
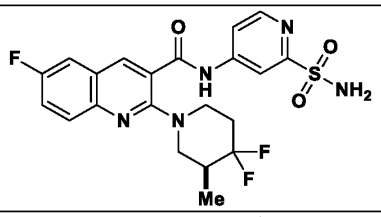
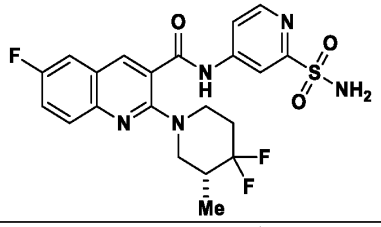
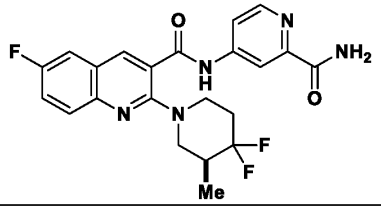
119	
120	
121	
122	
123	
124	

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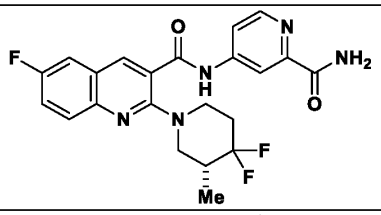
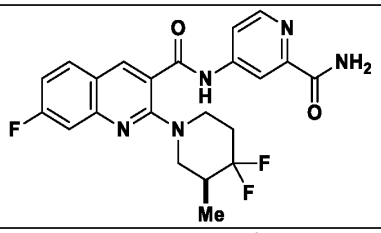
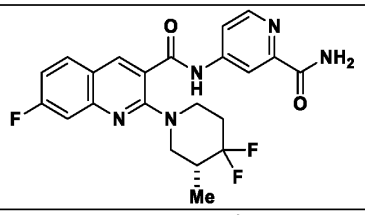
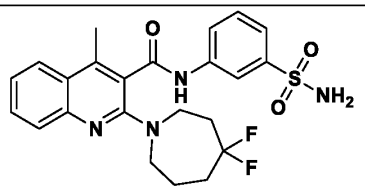
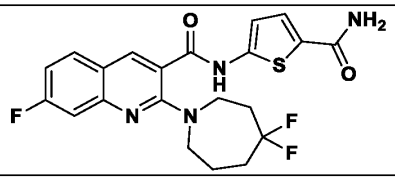
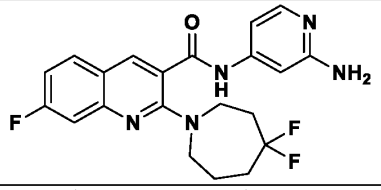
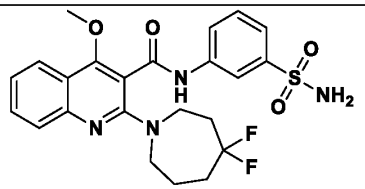
125	
126	
127	
128	
129	
130	
131	

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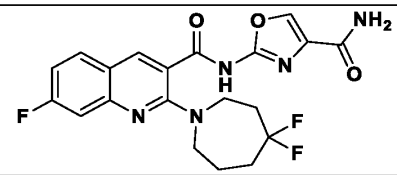
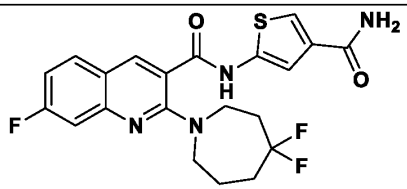
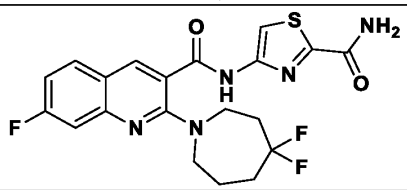
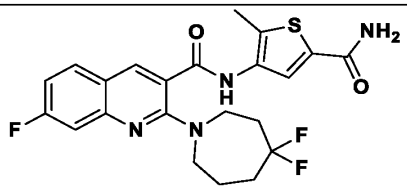
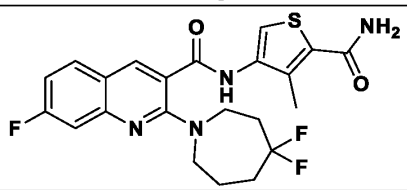
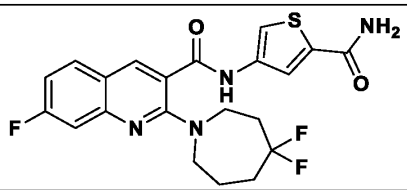
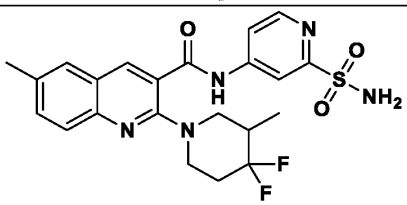
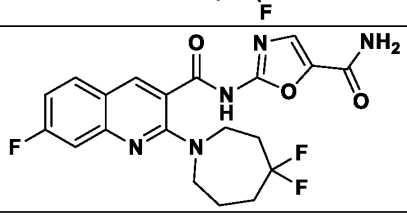
132	
133	
134	
135	
136	
137	
138	
139	

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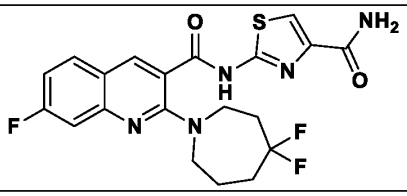
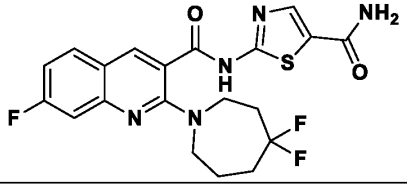
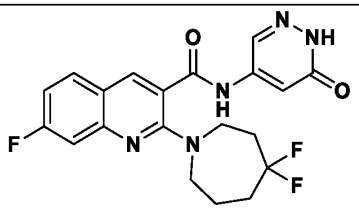
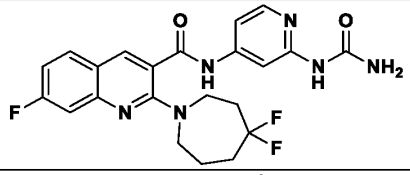
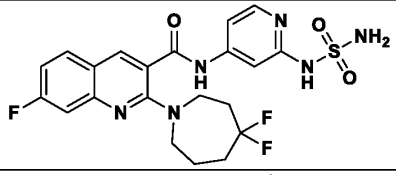
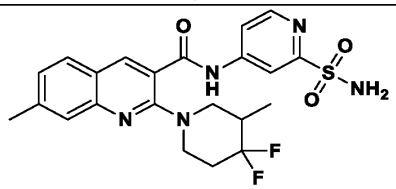
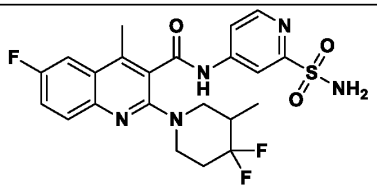
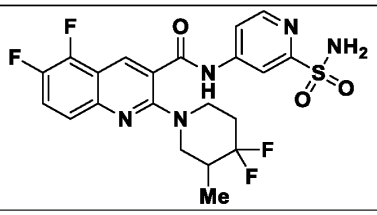
140	
141	
142	
143	
144	
145	
146	
147	

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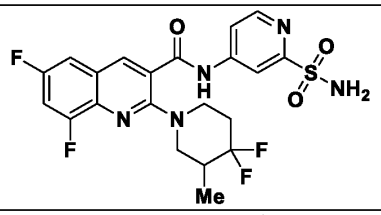
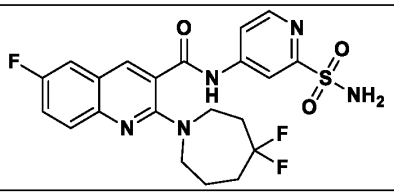
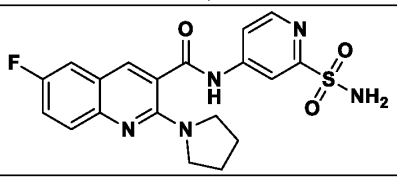
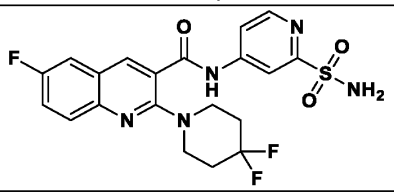
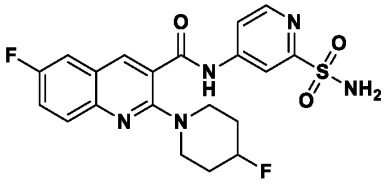
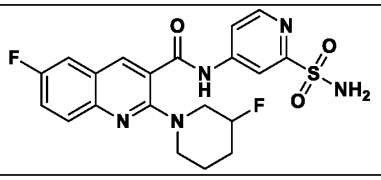
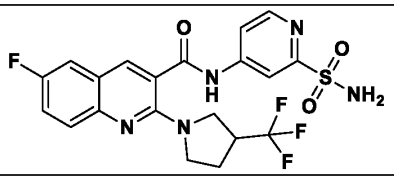
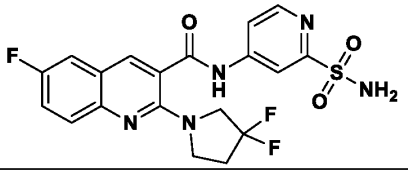
148	
149	
150	
151	
152	
153	
154	
155	

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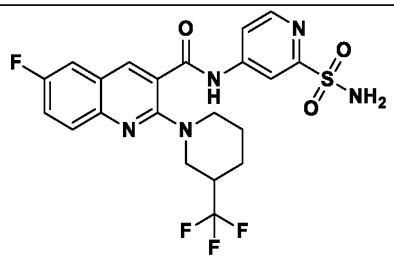
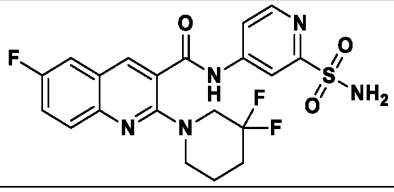
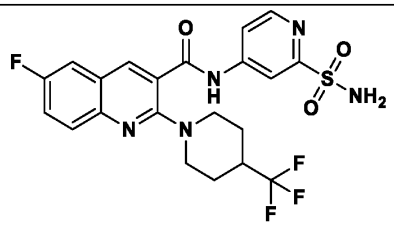
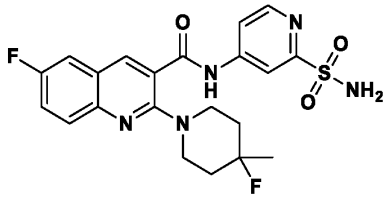
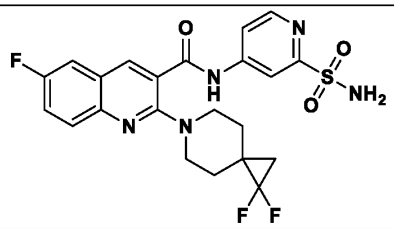
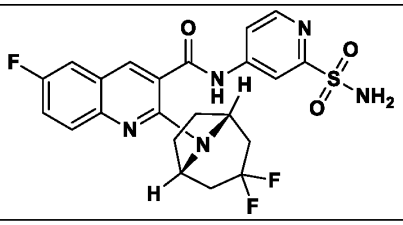
156	
157	
158	
159	
160	
161	

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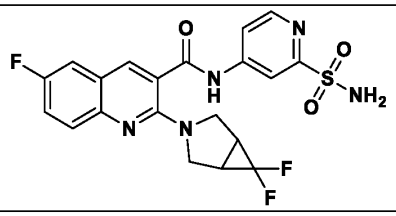
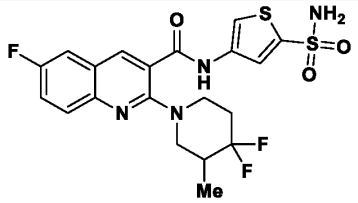
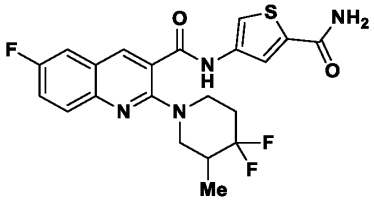
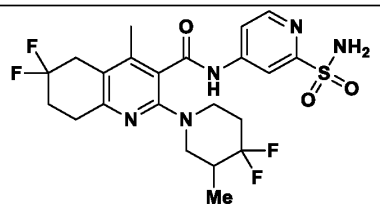
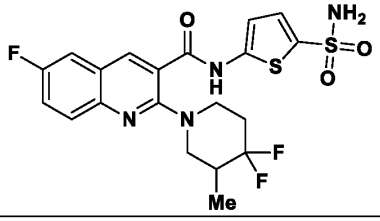
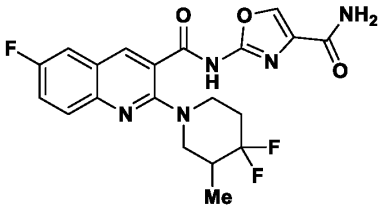
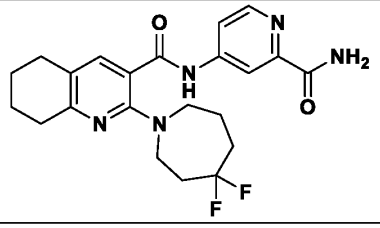
162	
163	
164	
165	
166	
167	
168	

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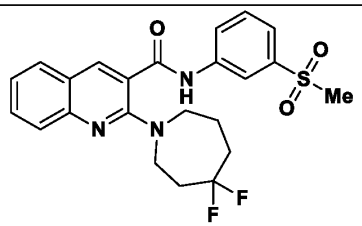
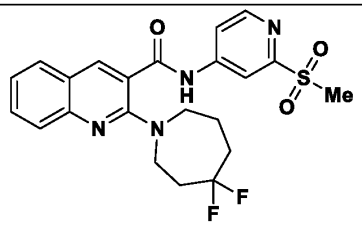
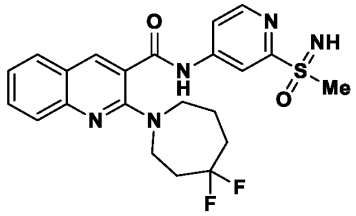
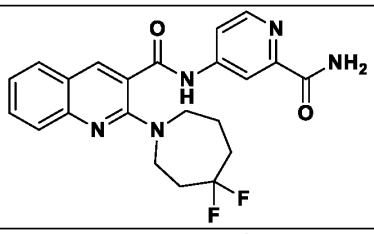
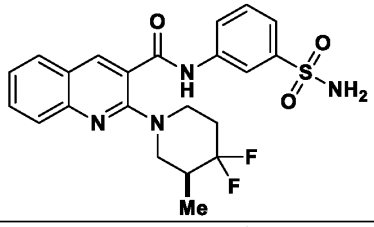
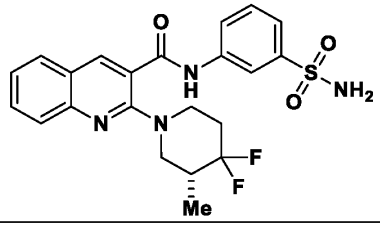
169	
170	
171	
172	
173	
174	

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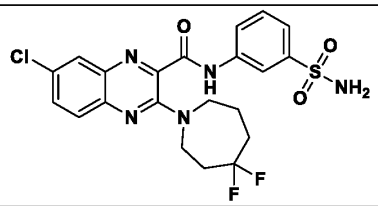
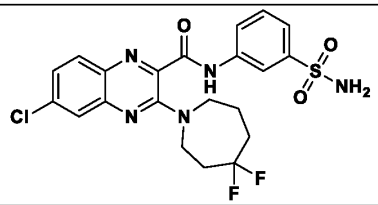
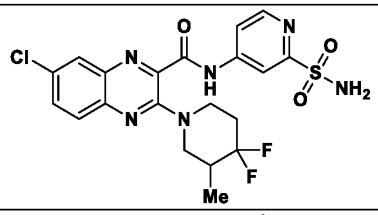
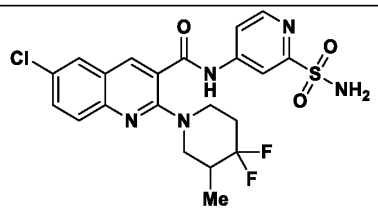
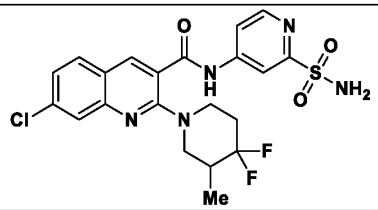
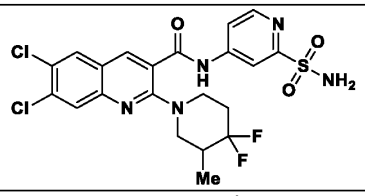
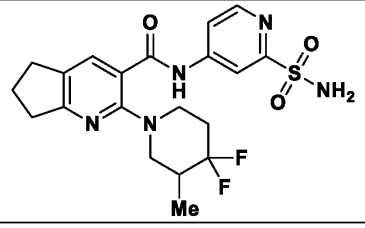
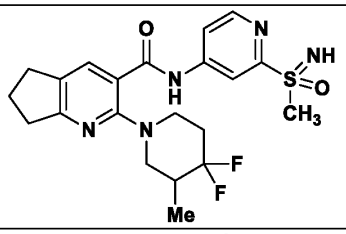
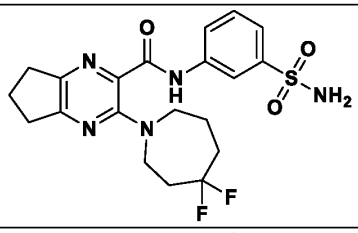
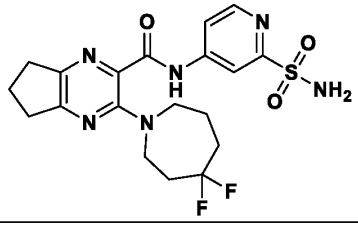
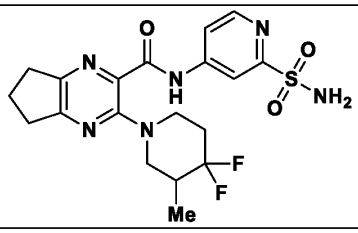
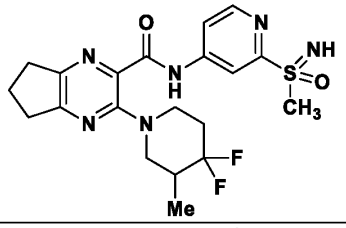
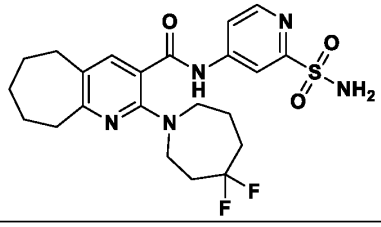
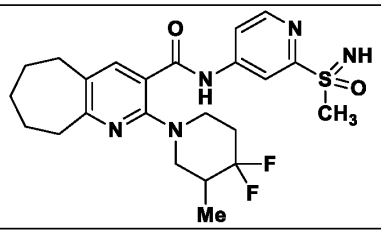
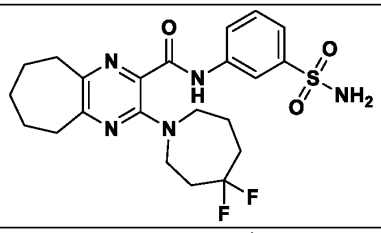
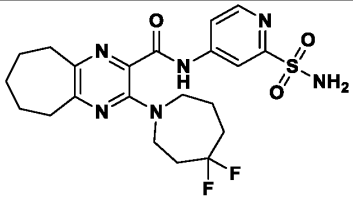
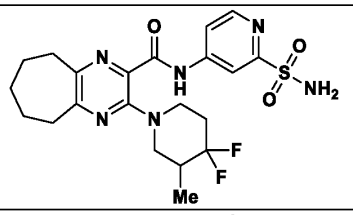
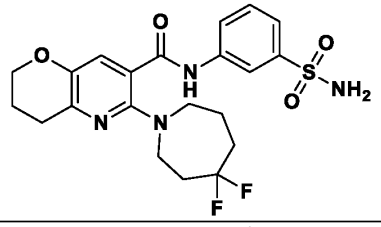
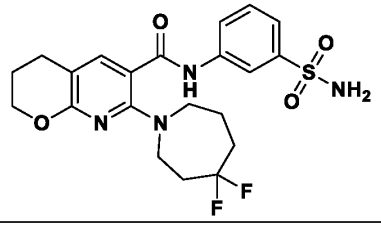
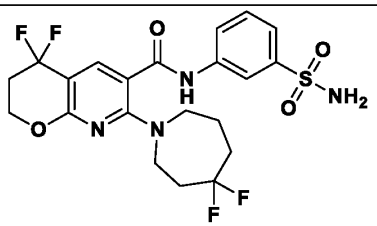
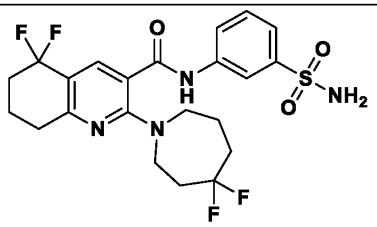
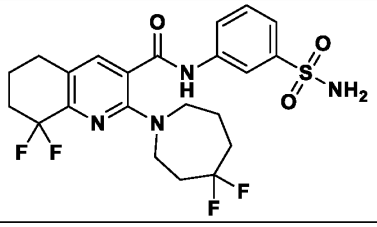
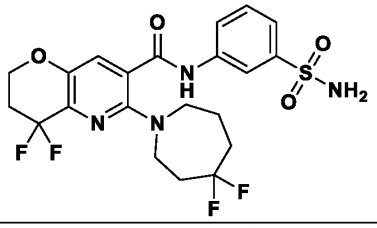
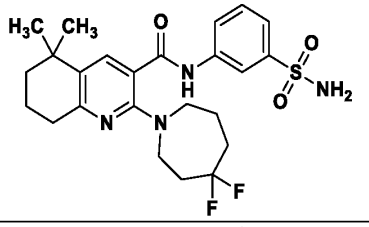
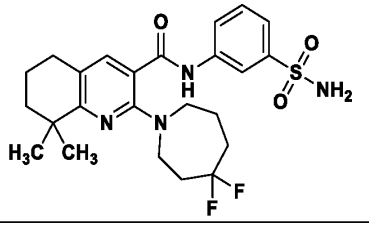
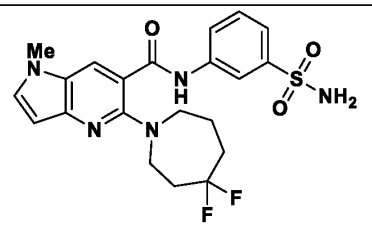
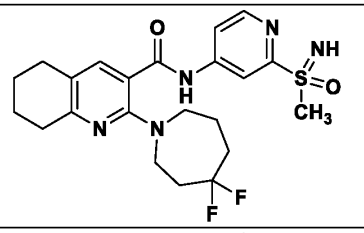
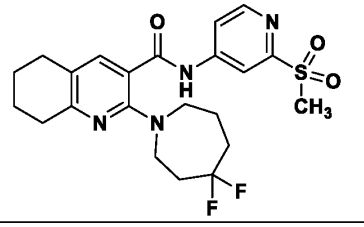
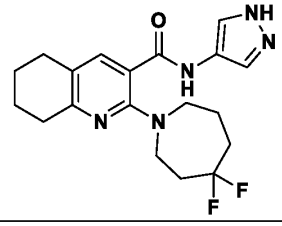
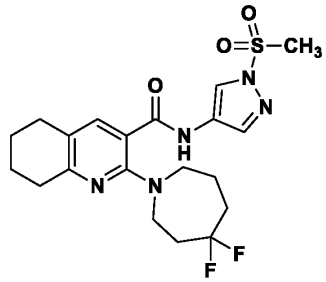
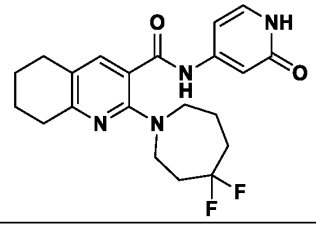
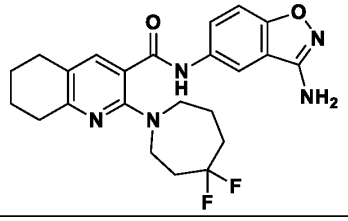
175	
176	
177	
178	
179	
180	
181	

Cmpd No.	Structure
182	
183	
184	
185	
186	
187	

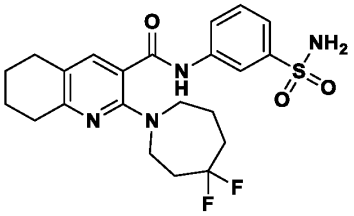
Cmpd No.	Structure
188	
189	
190	
191	
192	
193	

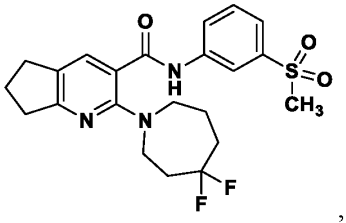
Cmpd No.	Structure
194	
195	
196	
197	
198	
199	

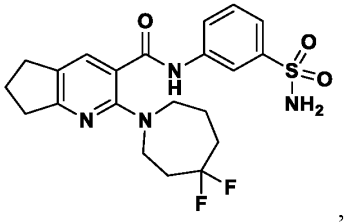
Cmpd No.	Structure
200	
201	
202	
203	
204	
205	

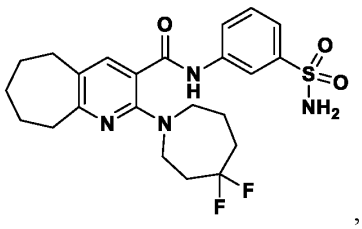
Cmpd No.	Structure
206	

[00127] Embodiment 19: Provided is a compound according to any aspect or embodiment disclosed herein, including any of embodiments 1-18, wherein the compound is not:

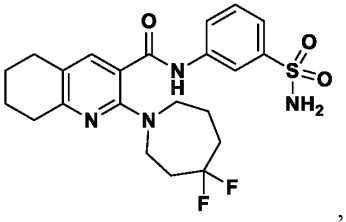
, 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

, 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

, 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

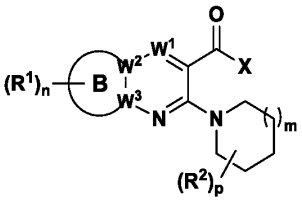
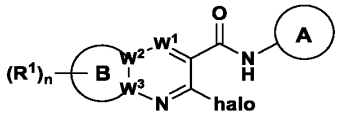
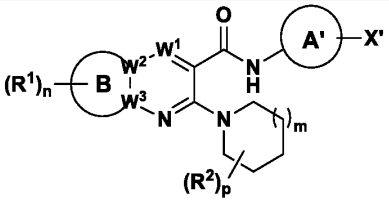
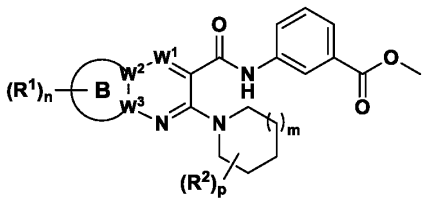


[00128] , 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof; or



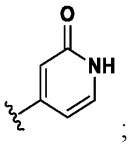
, 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00129] In some or any embodiments provided herein is a compound according to any one of the following formulas:

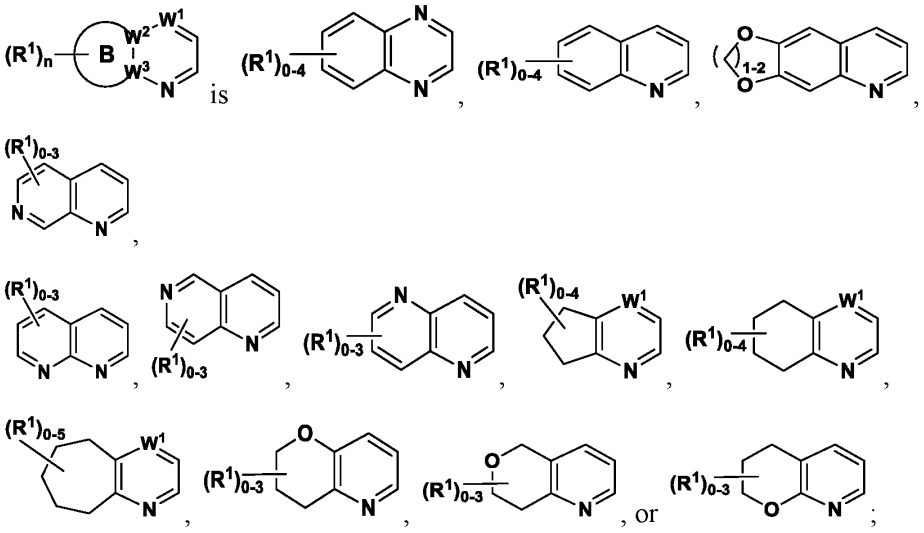
<table>
<tr>
<td>
(A)
where X is OH, OCH_3, OCH_2CH_3, or NH_2;</td>
<td>
(B);</td>
</tr>
<tr>
<td>
(C)
where X′ is SCH_3 or $S(O)CH_3$; and A′ is phenyl or pyridinyl; and</td>
<td>
(D);</td>
</tr>
</table>

or a salt thereof,

wherein

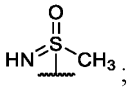
A is phenyl substituted with $\mathbf{R^3}$, pyridinyl substituted with $\mathbf{R^3}$, benzoisoxazolyl substituted with $\mathbf{R^3}$, unsubstituted pyrazolyl, pyrazolyl substituted with $\mathbf{R^3}$, or ;

$\mathbf{W^1}$ is -N= or -C(H)=;



each $\mathbf{R^1}$ is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, or halogen;

each $\mathbf{R^2}$ is independently hydrogen, C_1-C_6 alkyl, or halo;

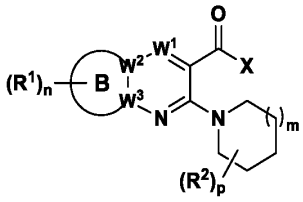
$\mathbf{R^3}$ is $-C(O)NH_2$, $-NH_2$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, or ;

m is 1 or 2;

n is 0, 1, or 2; and

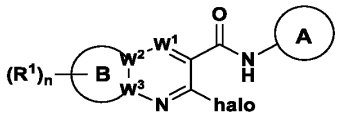
p is 0, 1, 2, or 3.

[00130] In one or more embodiments, provided herein is a compound according to any one of the following formulas:

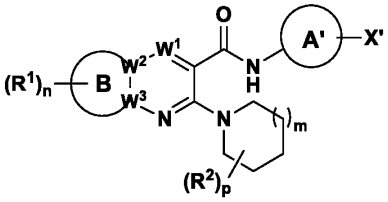


(A)

where **X** is OH, OCH_3, OCH_2CH_3, or NH_2;

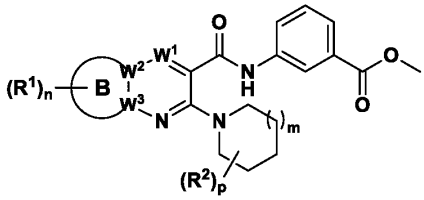


(B);



(C)

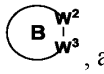
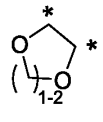
where **X′** is SCH_3 or $S(O)CH_3$; and **A′** is phenyl or pyridinyl; and

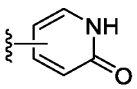


(D);

wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two **R^1** are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining **R^1** are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with **R^3** and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with **R^3** and optionally substituted with $(R^{3a})_q$; or  optionally substituted with $(R^{3a})_{q1}$;

W^1 is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C1-C6 alkoxy)=;

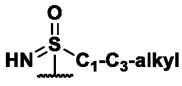
W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two R^2 are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two R^2 are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

R^3 is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(O)NH_2$, -$NHS(O)_2NH_2$, -$NHC(=NH)NH_2$, -$S(O)_2NHR$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

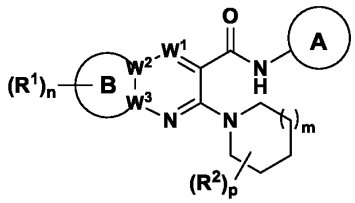
p is 0, 1, 2, 3, 4, 5, or 6

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3.

Additional Embodiments

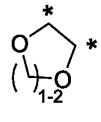
[00131] Embodiment 21: Provided are compounds as described herein, *e.g.*, of Formula (**I**):

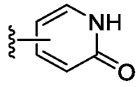


(I)

wherein

$\mathbf{R^1}$, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; or  optionally substituted with $(R^{3a})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

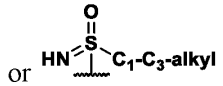
$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of **W²** and **W³** is -C- and the other is -N-, the dashed bond between **W²** and **W³** is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R², independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R²** are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R²**, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R²** are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R²**, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

R³ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(=NH)NH_2$, -$S(O)_2NH$**R**, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^3a, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

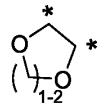
or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

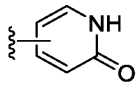
provided that the compound is not

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof; 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof; 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-

carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof; 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof; or 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00132] Embodiment 21a. Provided is a compound of Embodiment 21:, wherein:

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or wherein two **R^1** are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in ;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; or  optionally substituted with $(R^{3a})_{q1}$;

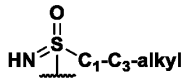
W^1 is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, or -C(cyclopropyl)=;

W^2 and **W^3** are each -C-, the dashed bond between **W^2** and **W^3** is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of **W^2** and **W^3** is -C- and the other is -N-, the dashed bond between **W^2** and **W^3** is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two **R^2** are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining **R^2**, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;$\mathbf{R^3}$ is hydrogen, -C(O)NH_2, -NH_2, -$S(O)_2$NH**R**, -$S(O)_2C_1$-C_6-alkyl, or 

, wherein **R** is hydrogen, C_1-C_3 alkyl or C_3-C_5 cycloalkyl;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

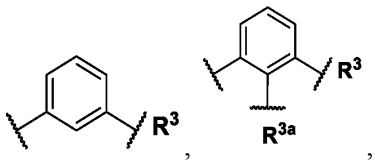
q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

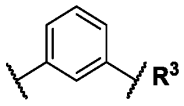
[00133] Embodiment 22. Provided is a compound of Embodiment 21 or 21a, wherein **A** is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, optionally wherein **A** is phenyl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00134] Embodiment 23. Provided is a compound of Embodiment 21, 21a, or 22, wherein **A** is phenyl substituted with $\mathbf{R^3}$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00135] Embodiment 24. Provided is a compound of Embodiment 21-23, wherein **A** is 

, wherein

designates attachment to $\mathbf{R^3}$; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

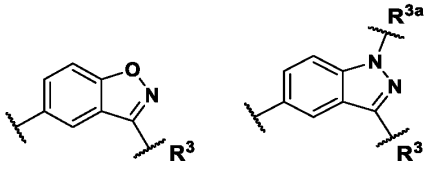
[00136] Embodiment 24a. Provided is a compound of Embodiment 21-24, wherein **A** is 

, wherein

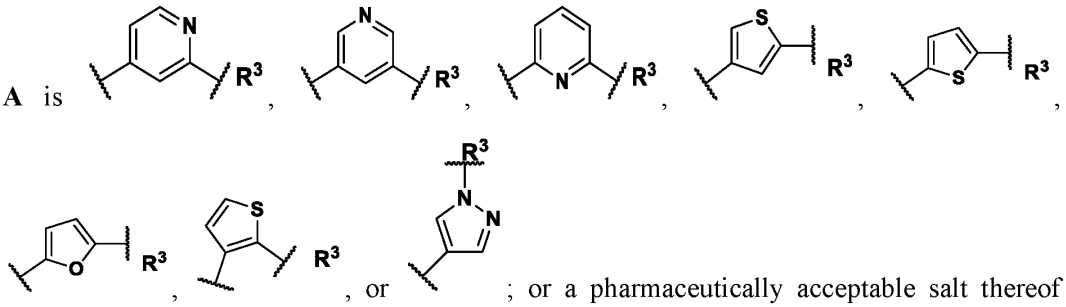
designates attachment to $\mathbf{R^3}$; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

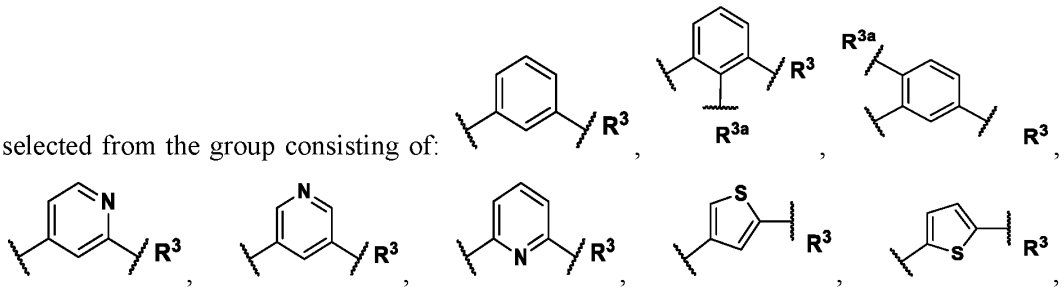
[00137] Embodiment 25. Provided is a compound of Embodiment 21, wherein **A** is 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, optionally

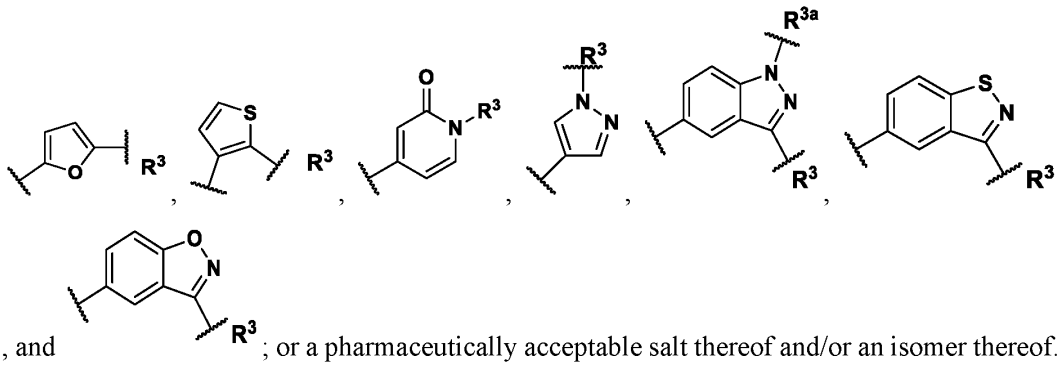
wherein **A** is 9-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, optionally wherein **A** is 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00138] Embodiment 25a. Provided is a compound of Embodiment 21 or 25, wherein **A** is ; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00139] Embodiment 26. 21 or 25, wherein **A** is 5- or 6-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, wherein **A** is 5-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or wherein **A** is 6-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

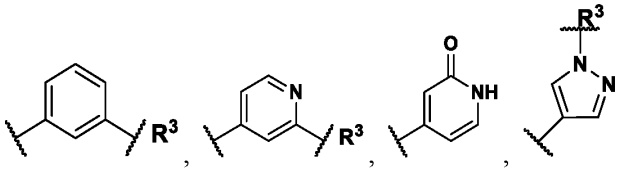
[00140] Embodiment 26a. Provided is a compound of Embodiment 21, 25, or 26, wherein **A** is ; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

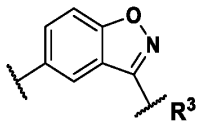
[00141] Embodiment 26b. Provided is a compound of Embodiment 21, wherein **A** is selected from the group consisting of: 



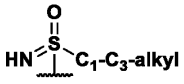
; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

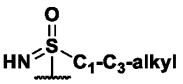
[00142] Embodiment 27. Provided is a compound of Embodiment 21, wherein **A** is selected from the group consisting of:





, wherein designates attachment to $\mathbf{R^3}$; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00143] Embodiment 28. Provided is a compound of any one of Embodiments 21-27, wherein $\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(=NH)NH_2$, -$S(O)_2NH\mathbf{R}$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00144] Embodiment 28a. Provided is a compound of any one of Embodiments 21-27, wherein $\mathbf{R^3}$ is -$C(O)NH_2$, -NH_2, -$S(O)_2NH\mathbf{R}$, -$S(O)_2C_1$-C_6-alkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl or C_3-C_5 cycloalkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00145] Embodiment 29. Provided is a compound of any one of Embodiments 21-27, wherein **A** is pyrazolyl and $\mathbf{R^3}$ is hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00146] Embodiment 30. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is $-C(O)NH_2$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00147] Embodiment 31. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is $-NH_2$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00148] Embodiment 32. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is $-S(O)_2NH\mathbf{R}$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

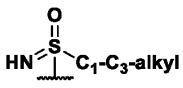
[00149] Embodiment 33. Provided is a compound of any one of Embodiments 21-29, wherein **R** is C_1-C_3 alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00150] Embodiment 34. Provided is a compound of any one of Embodiments 21-29, wherein **R** is C_3-C_5 cycloalkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

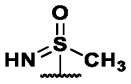
[00151] Embodiment 35. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is $-S(O)_2NH_2$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

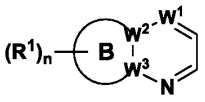
[00152] Embodiment 36. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is $-S(O)_2C_1$-C_6-alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

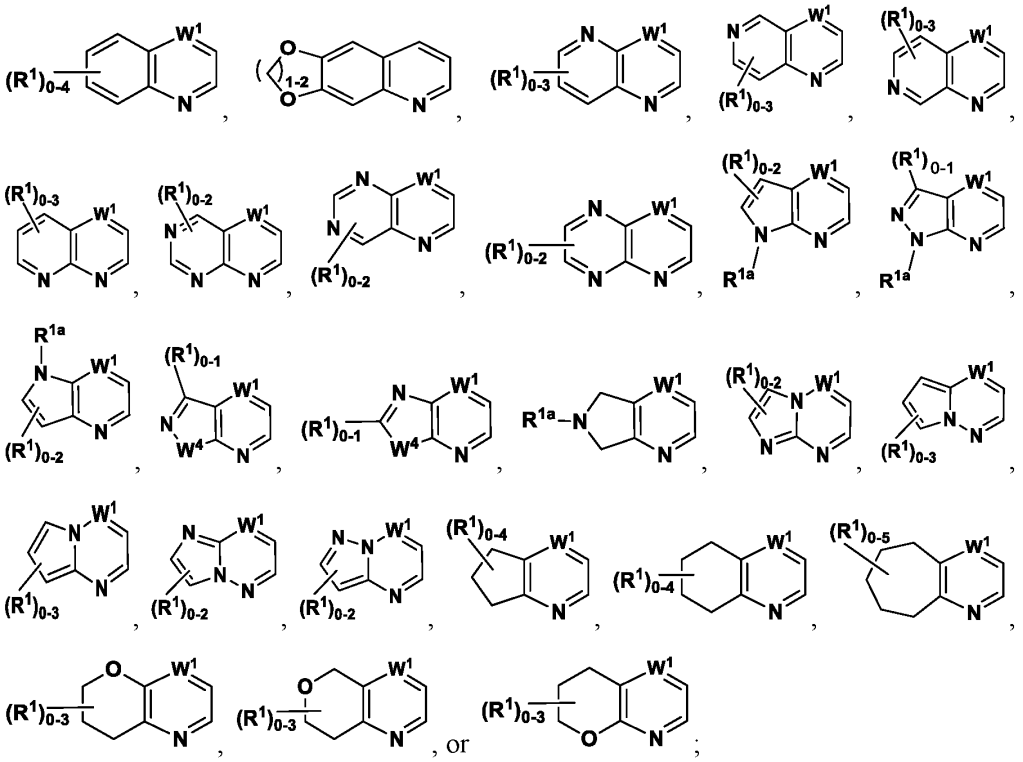
[00153] Embodiment 37. Provided is a compound of any one of Embodiments 21-28 and 36, wherein $\mathbf{R^3}$ is $-S(O)_2CH_3$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00154] Embodiment 38. Provided is a compound of any one of Embodiments 21-28, wherein $\mathbf{R^3}$ is 

, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00155] Embodiment 39. The Compound of claims Provided is a compound of any one of Embodiments 21-28 and 38, wherein $\mathbf{R^3}$ is , or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00156] Embodiment 40. Provided is a compound of any one of Embodiments 21-39, wherein  is

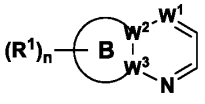


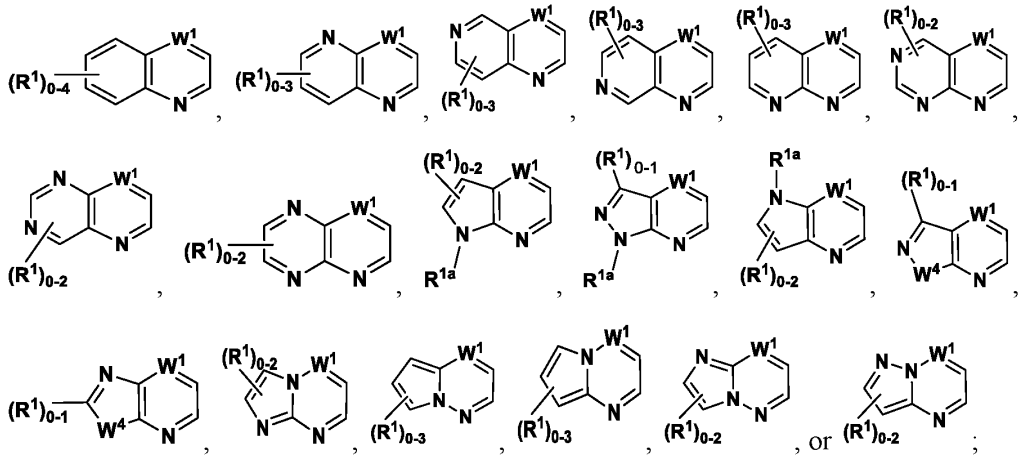
wherein $\mathbf{W^4}$ is O or S;

one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

$\mathbf{R^{1a}}$ is hydrogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00157] Embodiment 40a. Provided is a compound of any one of Embodiments 21-40, wherein  is

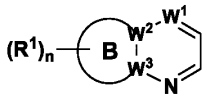


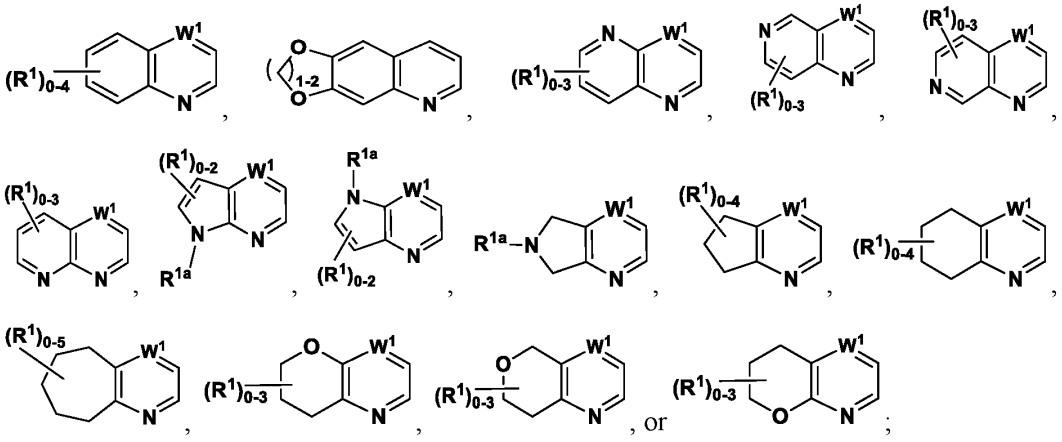
wherein W^4 is O or S;

one R^1 can be R^{1a} as indicated in the above rings; and

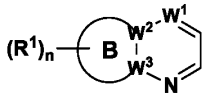
R^{1a} is hydrogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl;

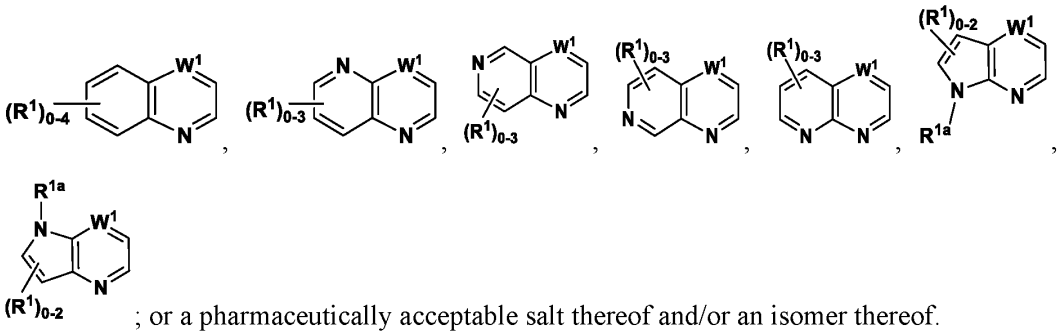
or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00158] Embodiment 41. Provided is a compound of any one of Embodiments 21-40, wherein  is



or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00159] Embodiment 41a. Provided is a compound of any one of Embodiments 21-40, wherein  is



; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00160] Embodiment 42. Provided is a compound of any one of Embodiments 40 and 41, wherein $\mathbf{R^{1a}}$ is hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00161] Embodiment 43. Provided is a compound of any one of Embodiments 40 and 41, wherein $\mathbf{R^{1a}}$ is C_1-C_6-alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00162] Embodiment 44. Provided is a compound of any one of Embodiments 40 and 41, wherein $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00163] Embodiment 45. Provided is a compound of any one of Embodiments 40 and 41, wherein $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkylC_1-C_3-alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00164] Embodiment 46. Provided is a compound of any one of Embodiments 21-45, wherein one $\mathbf{R^1}$ is present and is other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00165] Embodiment 47. Provided is a compound of any one of Embodiments 21-45, wherein two $\mathbf{R^1}$ are present and each is independently other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00166] Embodiment 48. Provided is a compound of any one of Embodiments 21-45, wherein three $\mathbf{R^1}$ are present and each is independently other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00167] Embodiment 49. Provided is a compound of any one of Embodiments 21-48, wherein at least one $\mathbf{R^1}$ is C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00168] Embodiment 50. Provided is a compound of any one of Embodiments 21-49, wherein at least one $\mathbf{R^1}$ is -CH_3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00169] Embodiment 51. Provided is a compound of any one of Embodiments 21-48, wherein at least one $\mathbf{R^1}$ is C_1-C_6 alkoxy, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00170] Embodiment 52. Provided is a compound of any one of Embodiments 21-48 and 51, wherein at least one $\mathbf{R^1}$ is -OCH_3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00171] Embodiment 53. Provided is a compound of any one of Embodiments 21-48, wherein at least one $\mathbf{R^1}$ is C_1-C_6 haloalkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00172] Embodiment 54. Provided is a compound of any one of Embodiments 21-48 and 53, wherein at least one $\mathbf{R^1}$ is -CF_3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00173] Embodiment 55. Provided is a compound of any one of Embodiments 21-48, wherein at least one $\mathbf{R^1}$ is halogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00174] Embodiment 56. Provided is a compound of any one of Embodiments 21-48 and 55, wherein at least one $\mathbf{R^1}$ is –Cl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

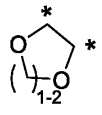
[00175] Embodiment 57. Provided is a compound of any one of Embodiments 21-48 and 55, wherein at least one $\mathbf{R^1}$ is –F, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00176] Embodiment 58. Provided is a compound of any one of Embodiments 21-48, wherein at least one $\mathbf{R^1}$ is halo-C_1-C_6 alkoxy, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00177] Embodiment 59. Provided is a compound of any one of Embodiments 21-48 and 58, wherein at least one $\mathbf{R^1}$ is -OCF_3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00178] Embodiment 60. Provided is a compound of any one of Embodiments 21-48, wherein each $\mathbf{R^1}$ is independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy, and halogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00179] Embodiment 61. Provided is a compound of any one of Embodiments 21-45, wherein each $\mathbf{R^1}$ is hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00180] Embodiment 61a. Provided is a compound of any one of Embodiments 21-48, wherein two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl.

[00181] Embodiment 62. Provided is a compound of any one of Embodiments 21-61, wherein one $\mathbf{R^2}$ is present and is other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00182] Embodiment 63. Provided is a compound of any one of Embodiments 21-61, wherein two $\mathbf{R^2}$ are present and each is independently other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00183] Embodiment 64. Provided is a compound of any one of Embodiments 21-61, wherein three $\mathbf{R^2}$ are present and each is independently other than hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00184] Embodiment 65. Provided is a compound of any one of Embodiments 21-64, wherein at least one $\mathbf{R^2}$ is halogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00185] Embodiment 66. Provided is a compound of any one of Embodiments 21-65, wherein at least one $\mathbf{R^2}$ is –F, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00186] Embodiment 67. Provided is a compound of any one of Embodiments 21-64, wherein at least one $\mathbf{R^2}$ is C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00187] Embodiment 68. Provided is a compound of any one of Embodiments 21-64 and 67, wherein at least one $\mathbf{R^2}$ is $-CH_3$, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00188] Embodiment 69. Provided is a compound of any one of Embodiments 21-61, 63, and 64, wherein two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00189] Embodiment 70. Provided is a compound of any one of Embodiments 21-61, 63, and 64 wherein two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 4- to 7-membered carbocyclic ring and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00190] Embodiment 71. Provided is a compound of any one of Embodiments 21-64 wherein each $\mathbf{R^2}$ is independently selected from C_1-C_6 alkyl and halogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00191] Embodiment 72. Provided is a compound of any one of Embodiments 21-71, wherein each $\mathbf{R^2}$ is hydrogen, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00192] Embodiment 73. Provided is a compound of any one of Embodiments 21-72, wherein **m** is 1 or 2, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00193] Embodiment 74. Provided is a compound of any one of Embodiments 21-73, wherein **m** is 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00194] Embodiment 75. Provided is a compound of any one of Embodiments 21-73, wherein **m** is 2, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00195] Embodiment 76. Provided is a compound of any one of Embodiments 21-75, wherein $\mathbf{W^1}$ is -N=, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00196] Embodiment 77. Provided is a compound of any one of Embodiments 21-75, wherein $\mathbf{W^1}$ is -C(H)=, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00197] Embodiment 78. Provided is a compound of any one of Embodiments 21-75, wherein $\mathbf{W^1}$ is -C(halogen)=, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00198] Embodiment 79. Provided is a compound of Embodiment 21-75, wherein $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00199] Embodiment 80. Provided is a compound of Embodiment 21-75, wherein $\mathbf{W^1}$ is -C(cyclopropyl)=, or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

[00200] Embodiment 81. Provided is a compound, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, selected from the group consisting of the compounds provided in Table A.

[00201] Embodiment 82. Provided is a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, and a pharmaceutically acceptable carrier.

[00202] Embodiment 83. Provided is the pharmaceutical composition of embodiment 82, wherein the composition is an oral or injectable composition.

[00203] Embodiment 84. Provided is the pharmaceutical composition of embodiment 83, wherein the injectable composition is a subcutaneously injectable composition.

[00204] Embodiment 85. Provided is method for the treatment of a condition associated with voltage-gated sodium channel function, including $Na_v1.8$, in a subject, comprising the administration of a therapeutically or prophylactically effective amount of the compound as disclosed herein, or the pharmaceutical composition of as disclosed herein.

[00205] Embodiment 86. Provided is the method of embodiment 85, wherein the subject is a human.

[00206] Embodiment 87. Provided is the method of embodiment 85 or 86, wherein the condition is pain or wherein the condition is associated with pain.

[00207] Embodiment 88. Provided is the method of embodiment 85 or 86, wherein the condition is pain.

[00208] Embodiment 89. Provided is the method of embodiment 85 or 86, wherein the condition is associated with pain.

[00209] Embodiment 90. Provided is the method of any one of embodiment 85 or 85-89, wherein the condition is selected from the group consisting of pain associated with erythromelalgia, pain associated with diabetic peripheral neuropathy, paroxysmal extreme pain

disorder, complex regional pain syndrome, pain associated with trigeminal neuralgia, pain associated with multiple sclerosis, pain associated with arthritis (including osteoarthritis), pain associated with postherpetic neuralgia, cancer pain, pain associated with cluster headache, pain associated with migraine, pain associated with sciatica, pain associated with endometriosis, pain associated with fibromyalgia, postsurgical pain, subacute pain, chronic pain, pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, pain associated with ocular surgery, pain associated with epilepsy, pain associated with Parkinson's disease, a mood disorder, psychosis, pain associated with amyotropic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

[00210] Embodiment 91. Provided is the method of embodiment 85 or 86, wherein the condition is selected from the group consisting of acute pain, subacute pain, post-surgical pain, and ocular pain.

[00211] Embodiment 92. Provided is a method of inhibiting $NA_v1.8$ comprising contacting $NA_v1.8$ with a compound as disclosed herein.

[00212] In some or any embodiments, provided herein are:

(a) compounds as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 and pharmaceutically acceptable salts and compositions thereof;

(b) compounds as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 and pharmaceutically acceptable salts and compositions thereof for use in the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(c) processes for the preparation of compounds as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 as described in more detail elsewhere herein;

(d) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(e) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or its pharmaceutically acceptable salt or composition;

(f) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or its pharmaceutically acceptable salt or composition;

(g) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or a pharmaceutically acceptable salt thereof together with one or more other effective agents for treating pain and/or conditions modulated by voltage-gated sodium channels, optionally in a pharmaceutically acceptable carrier or diluent;

(h) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(i) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain; and

(j) use of any compound described herein, *e.g.,* of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or a composition comprising any compound described herein, *e.g.,* of Formula (**I**) and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206 or a pharmaceutically acceptable salt or composition for the treatment of a condition associated with voltage-gated sodium channel function

described herein (e.g., pain), optionally in combination and/or alternation with one or more agent for the treatment of pain.

[00213] In some or any embodiments, provided herein are:

(a) compounds as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 and pharmaceutically acceptable salts and compositions thereof;

(b) compounds as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 and pharmaceutically acceptable salts and compositions thereof for use in the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(c) processes for the preparation of compounds as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 as described in more detail elsewhere herein;

(d) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(e) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or its pharmaceutically acceptable salt or composition;

(f) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or its pharmaceutically acceptable salt or composition;

(g) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or a pharmaceutically acceptable salt thereof together with one or more other effective agents for treating pain and/or conditions modulated by voltage-gated sodium channels, optionally in a pharmaceutically acceptable carrier or diluent;

(h) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent

for the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(i) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain; and

(j) use of any compound described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or a composition comprising any compound described herein, *e.g.,* of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206 or a pharmaceutically acceptable salt or composition for the treatment of a condition associated with voltage-gated sodium channel function described herein (e.g., pain), optionally in combination and/or alternation with one or more agent for the treatment of pain.

[00214] In some or any embodiments, provided herein are:

(a) compounds as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 and pharmaceutically acceptable salts and compositions thereof;

(b) compounds as described herein, *e.g.,* of Formula (**I**), and Compounds 1-206 and pharmaceutically acceptable salts and compositions thereof for use in the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(c) processes for the preparation of compounds as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 as described in more detail elsewhere herein;

(d) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(e) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or its pharmaceutically acceptable salt or composition;

(f) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein,

e.g., of Formula (**I**) and Compounds 1-206 or its pharmaceutically acceptable salt or composition;

(g) pharmaceutical formulations comprising a compound as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or a pharmaceutically acceptable salt thereof together with one or more other effective agents for treating pain and/or conditions modulated by voltage-gated sodium channels, optionally in a pharmaceutically acceptable carrier or diluent;

(h) a method for the treatment of pain in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain and/or conditions modulated by voltage-gated sodium channels;

(i) a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject that includes the administration of a therapeutically or prophylactically effective amount of a compound as described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more agent for the treatment of pain; and

(j) use of any compound described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or a composition comprising any compound described herein, *e.g.,* of Formula (**I**) and Compounds 1-206 or a pharmaceutically acceptable salt or composition for the treatment of a condition associated with voltage-gated sodium channel function described herein (e.g., pain), optionally in combination and/or alternation with one or more agent for the treatment of pain.

Optically Active Compounds

[00215] It is appreciated that compounds provided herein have several chiral centers and may exist in and be isolated in optically active and racemic forms. It is to be understood that any racemic, optically-active, diastereomeric, tautomeric, or stereoisomeric form, mixture, or combination thereof, of a compound provided herein, which possess the useful properties described herein is within the scope of the invention. It being well known in the art how to prepare optically active forms (in some or any embodiments, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[00216] In some or any embodiments, methods to obtain optically active materials are known in the art, and include at least the following.

i) physical separation of crystals - a technique whereby macroscopic crystals of the individual stereoisomers are manually separated. This technique can be used if crystals of the separate stereoisomers exist, *i.e.*, the material is a conglomerate, and the crystals are visually distinct;

ii) simultaneous crystallization - a technique whereby the individual stereoisomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) enzymatic resolutions - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the stereoisomers with an enzyme;

iv) enzymatic asymmetric synthesis - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an stereoisomerically pure or enriched synthetic precursor of the desired stereoisomer;

v) chemical asymmetric synthesis - a synthetic technique whereby the desired stereoisomer is synthesized from an achiral precursor under conditions that produce asymmetry (*i.e.*, chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound)

by virtue of unequal reaction rates of the stereoisomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) stereospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired stereoisomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography - a technique whereby the stereoisomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography - a technique whereby the racemate is volatilized and stereoisomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) extraction with chiral solvents - a technique whereby the stereoisomers are separated by virtue of preferential dissolution of one stereoisomer into a particular chiral solvent;

xiii) transport across chiral membranes - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one stereoisomer of the racemate to pass through.

[00217] In some or any embodiments, provided is a composition of a compound that comprises a substantially pure designated stereoisomer of the compound. In some or any embodiments, in the methods and compounds, the compounds are substantially free of other stereoisomer. In some or any embodiments, a composition includes a compound that is at least 85%, 90%, 95%, 98%, 99% or 100% by weight, of the designated stereoisomer, the remainder comprising other chemical species or stereoisomers.

Isotopically Enriched Compounds

[00218] Also provided herein are isotopically enriched compounds.

[00219] Isotopic enrichment (in some or any embodiments, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et. al.*,

Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky *et. al.*, J. Nat. Cancer Inst., 69: 1127 (1982); Mangold *et. al.*, Mutation Res. 308: 33 (1994); Gordon *et. al.*, Drug Metab. Dispos., 15: 589 (1987); Zello *et. al.*, Metabolism, 43: 487 (1994); Gately *et. al.*, J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999).

[00220] Isotopic enrichment of a drug can be used, in some or any embodiments, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrees the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[00221] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C–H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). See, *e.g.,* Foster *et al.*, Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.*, Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999).

[00222] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C–H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

[00223] Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in

very low concentrations, most commonly found as T_2O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S, or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen, may lead to a similar kinetic isotope effect.

[00224] For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity.

[00225] In some embodiments, the compounds described herein may be used as radiopharmaceuticals such as, for example, imaging agents. In one instance, radiopharmaceuticals are positron emission tomography (PET) imaging agents. In such embodiments, substitution of radionuclides (e.g., positron emitting isotopes) for atoms in the compounds allows for the syntheses of radiopharmaceuticals that can function as imaging agents. In some embodiments, radionuclides which can be substituted in the compounds described herein include, and are not limited to, ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{76}Br, and ^{124}I. In some embodiments, the compound is isotopically enriched at one or more atoms, one atom, two atoms, or three atoms. In some embodiments, the compound is administered as an isotopic composition.

[00226] The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. In some or any embodiments, such enzymes include the cytochrome P450 enzymes ("CYPs"), esterases,

proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

[00227] Therefore, isotopic enrichment at certain positions of a compound provided herein will produce a detectable KIE that will affect the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition.

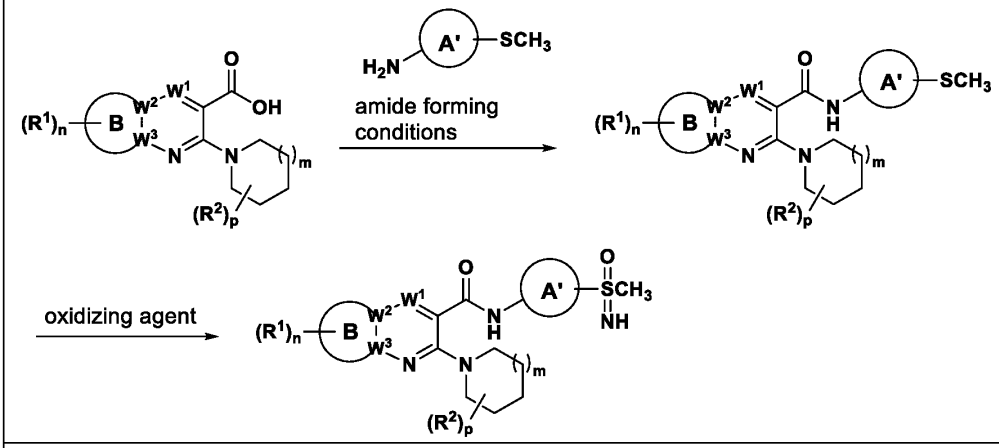
Preparation of Compounds

[00228] The compounds provided herein can be prepared, isolated or obtained by any method apparent to those of skill in the art. Compounds provided herein can be prepared according to the Exemplary Preparation Schemes provided below. Reaction conditions, steps and reactants not provided in the Exemplary Preparation Schemes would be apparent to, and known by, those skilled in the art.

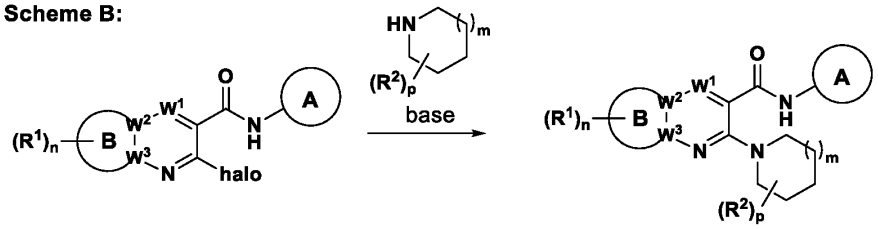
[00229] Additional steps and reagents not provided in the Exemplary Preparation Scheme would be known to those of skill in the art. For example, intermediates and compounds could be prepared using the procedures known by one of ordinary skill in the art or as disclosed in International Patent Application Nos. PCT/US2019/058251 and PCT/US2019/058999 (wherein the synthetic methods disclosed therein are herein incorporated by reference in their entirety). Exemplary methods of preparation are described in detail in the Examples herein.

[00230] In one or more embodiments, provided herein is a method of preparing a compound herein according to any of the following schemes:

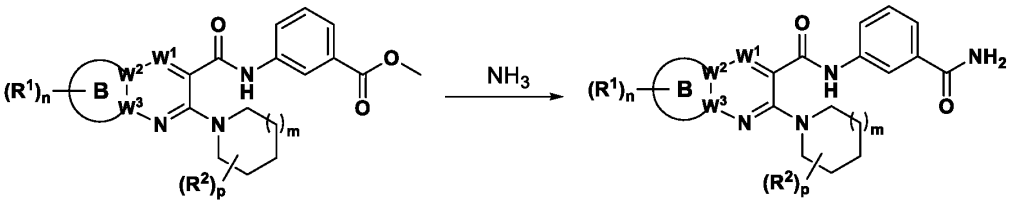
Scheme A:



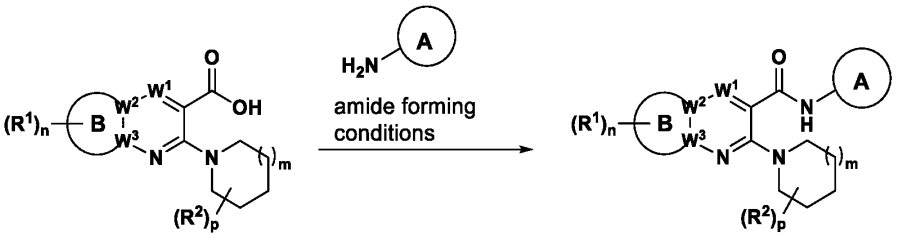
Scheme B:

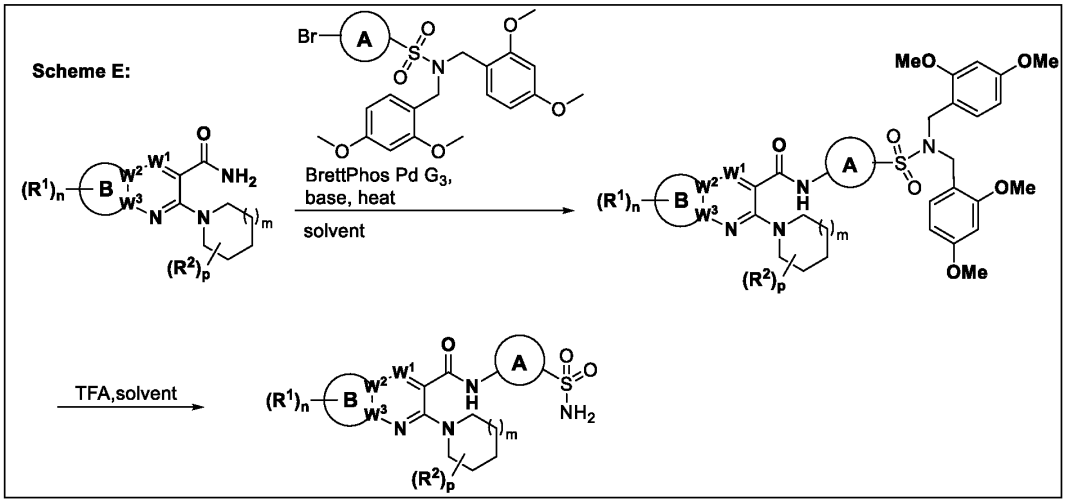


Scheme C:



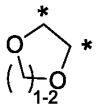
Scheme D:

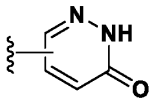


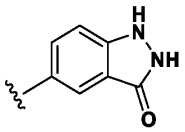


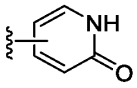
wherein

$\mathbf{R^1}$, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

wherein two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$; 

optionally substituted with $(R^{3a})_{q1}$;  optionally substituted with $(R^{3a})_{q1}$; or

 optionally substituted with $(\mathbf{R^{3a}})_{q1}$;

W^1 is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C1-C6 alkoxy)=;

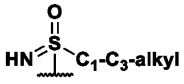
W^2 and W^3 are each -C-, the dashed bond between W^2 and W^3 is a double bond, and  is a partially unsaturated 5 to 7-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of W^2 and W^3 is -C- and the other is -N-, the dashed bond between W^2 and W^3 is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

R^2, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or

two R^2 are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two R^2 are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining R^2, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

R^3 is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -C(=NH)NH_2, -C(O)NH_2, -NH_2, -NHC(O)$C_{1\text{-}3}$alkyl, -NHC(O)NH_2, -$NHS(O)_2NH_2$, -NHC(=NH)NH_2, -$S(O)_2$NH**R**, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

, wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

R^{3a}, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

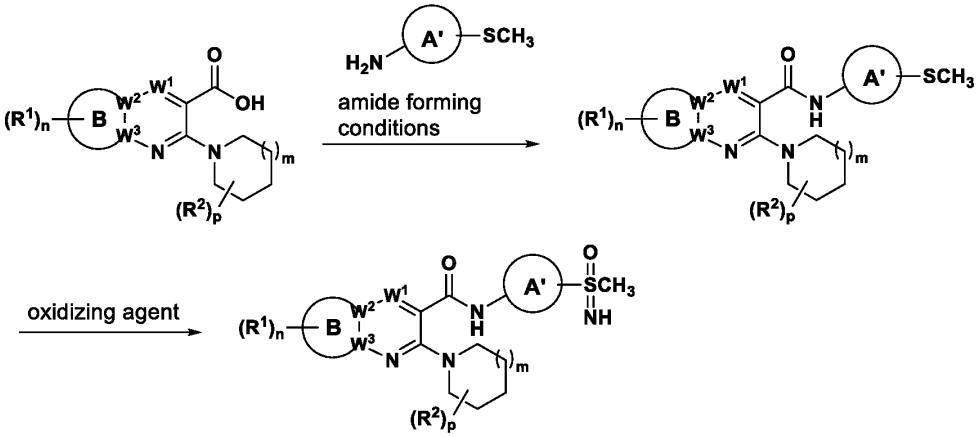
q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3;

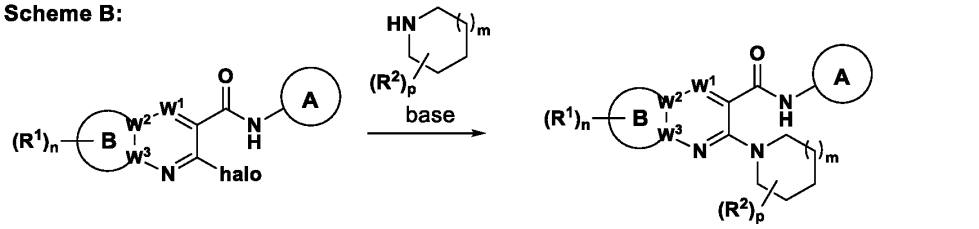
to yield a compound as disclosed herein, or a pharmaceutically acceptable salt thereof and/or an isomer thereof; and optionally isolating the compound as disclosed herein.

[00231] In one or more embodiments, provided herein is a method of preparing a compound as disclosed herein according to any of the following schemes:

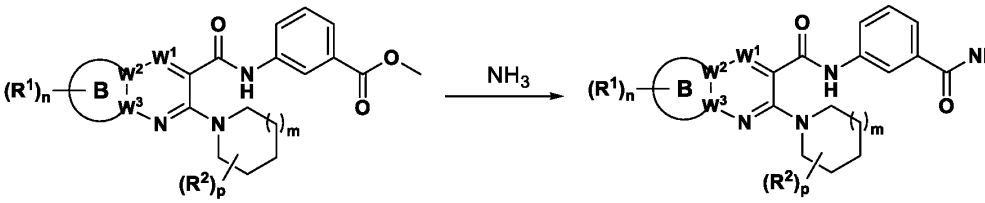
Scheme A:



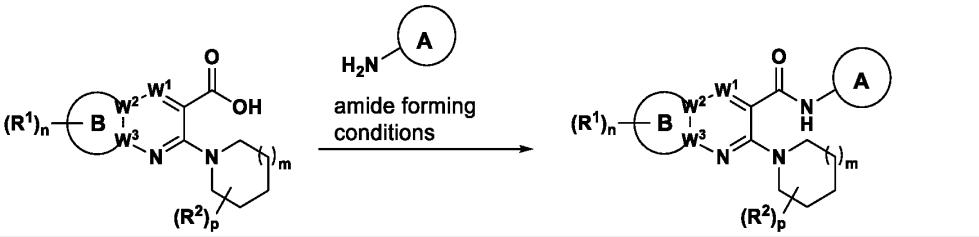
Scheme B:

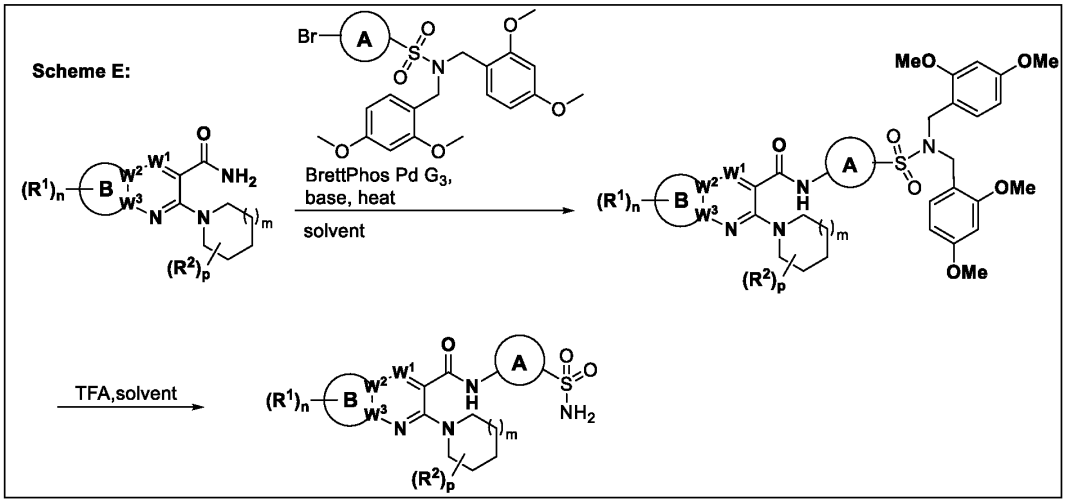


Scheme C:

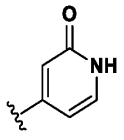


Scheme D:

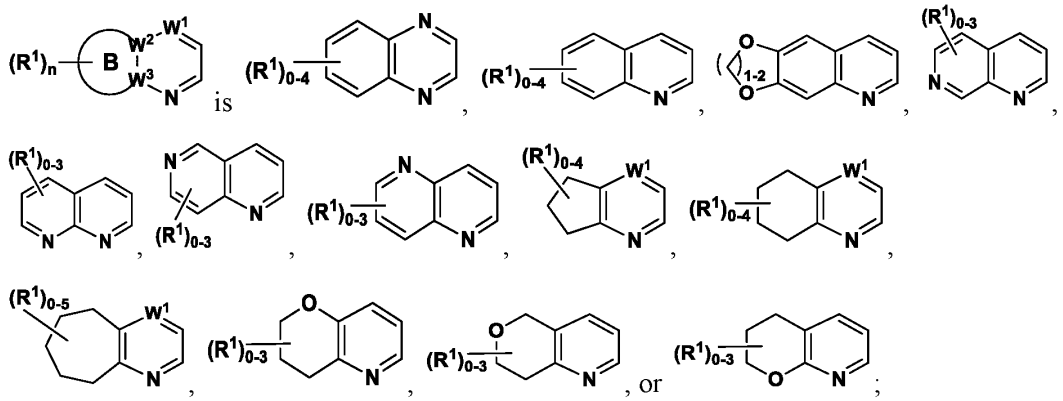




wherein

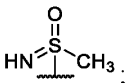
A is phenyl substituted with R^3, pyridinyl substituted with R^3, benzoisoxazolyl substituted with R^3, unsubstituted pyrazolyl, pyrazolyl substituted with R^3, or ;

W^1 is -N= or -C(H)=;



each R^1 is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, or halogen;

each R^2 is independently hydrogen, C_1-C_6 alkyl, or halo;

R^3 is -C(O)NH_2, -NH_2, -S(O)$_2NH_2$, -S(O)$_2CH_3$, or ;

m is 1 or 2;

n is 0, 1, or 2; and

p is 0, 1, 2, or 3;

to yield a compound as disclosed herein; and

b) optionally isolating the compound as disclosed herein.

[00232] One of skill will understand that the order of steps for any process described herein may be changed. Other variations will be apparent to one of skill in the art and all such variations are contemplated within the scope of embodiments presented herein.

Pharmaceutical Compositions and Methods of Administration

[00233] The compounds provided herein can be formulated into pharmaceutical compositions using methods available in the art and those disclosed herein. Any of the compounds disclosed herein can be provided in the appropriate pharmaceutical composition and be administered by a suitable route of administration. Provided herein are pharmaceutical compositions comprising a compound of Formula (**I**), (**I-P1**), or (**I-P2**), as described herein in some and any embodiments, and a pharmaceutically acceptable carrier. In some embodiments, the composition is an oral or injectable composition. In some of such embodiments, the injectable composition is a subcutaneously injectable composition.

[00234] The methods provided herein encompass administering pharmaceutical compositions containing at least one compound as described herein, including a compound of Formula (**I**), (**I-P1**), or (**I-P2**), if appropriate in a salt form, either used alone or in the form of a combination with one or more compatible and pharmaceutically acceptable carriers, such as diluents or adjuvants, or with another agent for the treatment of pain and/or conditions modulated by voltage-gated sodium channels.

[00235] In some or any embodiments, the second agent can be formulated or packaged with the compound provided herein. Of course, the second agent will only be formulated with the compound provided herein when, according to the judgment of those of skill in the art, such co-formulation should not interfere with the activity of either agent or the method of administration. In some or any embodiments, the compound provided herein and the second agent are formulated separately. They can be packaged together, or packaged separately, for the convenience of the practitioner of skill in the art.

[00236] In clinical practice the active agents provided herein may be administered by any conventional route, in particular orally, parenterally, rectally or by inhalation (*e.g.* in the form

of aerosols). In some or any embodiments, the compound provided herein is administered orally.

[00237] Use may be made, as solid compositions for oral administration, of tablets, pills, hard gelatin capsules, powders or granules. In these compositions, the active product is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose or starch.

[00238] These compositions can comprise substances other than diluents, for example a lubricant, such as magnesium stearate, or a coating intended for controlled release.

[00239] Use may be made, as liquid compositions for oral administration, of solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents, such as water or liquid paraffin. These compositions can also comprise substances other than diluents, in some or any embodiments, wetting, sweetening or flavoring products.

[00240] The compositions for parenteral administration can be emulsions or sterile solutions. Use may be made, as solvent or vehicle, of propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, in some or any embodiments, ethyl oleate. These compositions can also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization can be carried out in several ways, in some or any embodiments, using a bacteriological filter, by radiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

[00241] The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active principle, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

[00242] The compositions can also be aerosols. For use in the form of liquid aerosols, the compositions can be stable sterile solutions or solid compositions dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active principle is finely divided and combined with a water-soluble solid diluent or vehicle, in some or any embodiments, dextran, mannitol or lactose.

[00243] In some or any embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, a compound provided herein, or other

prophylactic or therapeutic agent), and a typically one or more pharmaceutically acceptable carriers or excipients. In a specific embodiment and in this context, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" includes a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water can be used as a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Examples of suitable pharmaceutical carriers are described in Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00244] Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and in some or any embodiments, suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a subject and the specific active ingredients in the dosage form. The composition or single unit dosage form, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[00245] Lactose free compositions provided herein can comprise excipients that are well known in the art and are listed, in some or any embodiments, in the U.S. Pharmacopeia (USP 36–NF 31 S2). In general, lactose free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose free dosage forms comprise an active ingredient, microcrystalline cellulose, pre gelatinized starch, and magnesium stearate.

[00246] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the

pharmaceutical arts as a means of simulating long term storage in order to determine characteristics such as shelf life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, New York, 1995, pp. 379 80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00247] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00248] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. In some or any embodiments, suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00249] Further provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00250] The pharmaceutical compositions and single unit dosage forms can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions and dosage forms will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent, in some or any embodiments, in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration. In a some or any embodiment, the pharmaceutical compositions or single

unit dosage forms are sterile and in suitable form for administration to a subject, in some or any embodiments, an animal subject, such as a mammalian subject, in some or any embodiments, a human subject.

[00251] A pharmaceutical composition is formulated to be compatible with its intended route of administration. In some or any embodiments, routes of administration include, but are not limited to, parenteral, *e.g.*, intrathecal, epidural, local or regional for peripheral nerve block, intravenous, intradermal, subcutaneous, intramuscular, subcutaneous, oral, buccal, sublingual, inhalation, intranasal, transdermal, topical (including administration to the eye, and in some embodiments to the cornea), transmucosal, intra-tumoral, intra-synovial, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical (including administration to the eye, and in some embodiments to the cornea) administration to human beings. In a specific embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

[00252] In some or any embodiments, dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a subject, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil in water emulsions, or a water in oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a subject; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a subject.

[00253] The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. In some or any embodiments, a dosage form used in the initial treatment of pain may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the maintenance treatment of the same infection. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active

ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed herein will vary from one another will be readily apparent to those skilled in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00254] Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, in some or any embodiments, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachet indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[00255] Typical dosage forms comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day taken with food. Particular dosage forms can have about 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 100, 200, 250, 500 or 1000 mg of the active compound.

Oral Dosage Forms

[00256] Pharmaceutical compositions that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00257] In some or any embodiments, the oral dosage forms are solid and prepared under anhydrous conditions with anhydrous ingredients, as described in detail herein. However, the scope of the compositions provided herein extends beyond anhydrous, solid oral dosage forms. As such, further forms are described herein.

[00258] Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form

of preparation desired for administration. In some or any embodiments, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. In some or any embodiments, excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00259] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00260] In some or any embodiments, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00261] In some or any embodiments, excipients that can be used in oral dosage forms include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[00262] In some or any embodiments, fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre gelatinized starch, and mixtures thereof. The

binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00263] In some or any embodiments, suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103 AVICEL RC 581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC 581. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103™ and Starch 1500 LM.

[00264] Disintegrants are used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[00265] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[00266] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, in some or any embodiments, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all,

lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

[00267] Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. In some or any embodiments, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500; each of which is incorporated herein by reference in its entirety. Such dosage forms can be used to provide slow or controlled release of one or more active ingredients using, in some or any embodiments, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein. Thus encompassed herein are unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gel caps, and caplets that are adapted for controlled release.

[00268] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00269] Most controlled release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or

prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[00270] In some or any embodiments, the drug may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In some or any embodiments, a pump may be used (*see,* Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, *i.e.*, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, *Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984)). Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)). The active ingredient can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

Parenteral Dosage Forms

[00271] In some or any embodiments, provided are parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. In some or any embodiments, parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[00272] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. In some or any embodiments, suitable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00273] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms.

Transdermal, Topical & Mucosal Dosage Forms

[00274] Also provided are transdermal, topical, and mucosal dosage forms. Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[00275] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed herein are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane 1,3 diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are nontoxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy; Pharmaceutical Press; 22 edition (September 15, 2012).

[00276] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients provided. In some or any embodiments, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[00277] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery enhancing or penetration enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Dosage and Unit Dosage Forms

[00278] In human therapeutics, the doctor will determine the posology which the doctor considers most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the infection and other factors specific to the subject to be treated. In some or any embodiments, doses are from about 1 to about 1000 mg per day for an adult, or from about 5 to about 250 mg per day or from about 10 to 50 mg per day for an adult. In some or any embodiments, doses are from about 5 to about 400 mg per day or 25 to 200 mg per day per adult. In some or any embodiments, dose rates of from about 50 to about 500 mg per day are also contemplated. In some or any embodiments, doses for subcutaneous administration are from about 1 to about 50 mg per day, or from about 1 to about 25 mg per day, or from about 1 to about 10 mg per day, or from about 1 to about 20 mg per day, or from about 5 to about 25 mg per day, or from about 5 mg to about 20 mg per day, or from about 10 to about 20 mg per day. In some or any embodiments, doses for oral administration are from about 5 to about 250 mg per day, from about 5 to 200 mg per day, or from about 50 mg to about 100 mg per day, or from about 75 mg to about 1125 mg per day, or from about 10 mg to about 200 mg per day. In some embodiments, the mg/day amounts are for an adult. In further aspects, provided are methods of treating a condition associated with voltage-gated sodium channel function and/or pain in a subject by administering, to a subject in need thereof, a therapeutically or prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. The amount of the compound or composition which will be therapeutically or prophylactically effective in the treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00279] In some or any embodiments, exemplary doses of a composition include milligram or microgram amounts of the active compound per kilogram of subject or sample weight (*e.g.*, about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to

about 10 milligrams per kilogram). For compositions provided herein, in some or any embodiments, the dosage administered to a subject is 0.01 mg/kg to 3 mg/kg of the subject's body weight, or 0.10 mg/kg to 3 mg/kg of the subject's body weight, based on weight of the active compound. In some or any embodiments, the dosage administered to a subject is between 0.20 mg/kg and 2.00 mg/kg, or between 0.30 mg/kg and 1.50 mg/kg of the subject's body weight. In some embodiments, the dosage is administered subcutaneously to a subject and is between about 0.01 mg/kg to 1 mg/kg (inclusive), or between about 0.03 mg/kg to 0.5 mg/kg (inclusive) of the subject's body weight, based on weight of the active compound. In some embodiments, the dosage is administered orally to a subject and is between about 0.10 mg/kg to 5 mg/kg (inclusive) of the subject's body weight, or between about 0.10 mg/kg to 2 mg/kg (inclusive) of the subject's body weight, based on weight of the active compound.

[00280] In some or any embodiments, the recommended daily dose range of a composition provided herein for the conditions described herein lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose or as divided doses throughout a day. In some or any embodiments, the daily dose is administered twice daily in equally divided doses. In some or any embodiments, the daily dose is administered thrice daily in equally divided doses. In some or any embodiments, the daily dose is administered four times daily in equally divided doses. In some or any embodiments, a daily dose range should be from about 0.01 mg to about 400 mg per day, from about 0.1 mg to about 250 mg per day, from about 10 mg to about 200 mg per day, in other embodiments, or from about 10 mg and about 150 mg per day, in further embodiments, between about 25 and about 100 mg per day. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

[00281] Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the composition provided herein are also encompassed by the herein described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. In some or any embodiments, the dosage administered to the

subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[00282] In some or any embodiment, the dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 10 mg/kg, or 15 mg/kg or more of a subject's body weight. In another embodiment, the dosage of the composition or a composition provided herein administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is a unit dose of 0.1 mg to 200 mg, 0.1 mg to 100 mg, 0.1 mg to 50 mg, 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 10 mg, 0.1 mg to 7.5 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 mg to 7.5 mg, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 7.5 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

[00283] In some or any embodiments, treatment or prevention can be initiated with one or more loading doses of a compound or composition provided herein followed by one or more maintenance doses. In such embodiments, the loading dose can be, for instance, about 6 to about 40 mg per day, or about 10 to about 20 mg per day for one day to five weeks. The loading dose can be followed by one or more maintenance doses. In some or any embodiments, each maintenance does is, independently, about from about 1 mg to about 20 mg per day, between about 2.5 mg and about 15 mg per day, or between about 2.5 and about 8 mg per day. Maintenance doses can be administered daily and can be administered as single doses, or as divided doses.

[00284] In some or any embodiments, a dose of a compound or composition provided herein can be administered to achieve a steady-state concentration of the active ingredient in blood or serum of the subject. The steady-state concentration can be determined by measurement according to techniques available to those of skill or can be based on the physical characteristics of the subject such as height, weight and age. In some or any embodiments, a sufficient amount of a compound or composition provided herein is administered to achieve a steady-state concentration in blood or serum of the subject of from about 100 to about 1000 ng/mL, from about 150 to about 800 ng/mL, or from about 300 to about 600 ng/mL. In some or any embodiments, loading doses can be administered to achieve steady-state blood or serum

concentrations of about 300 to about 2000 ng/mL, or about 400 to about 800 ng/mL for one to five days. In some or any embodiments, maintenance doses can be administered to achieve a steady-state concentration in blood or serum of the subject of from about 100 to about 1000 ng/mL, from about 150 to about 800 ng/mL, or from about 300 to about 600 ng/mL. In some or any embodiments, administration of the same composition may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00285] In some or any embodiments, provided herein are unit dosages comprising a compound, or a pharmaceutically acceptable salt thereof, in a form suitable for administration. Such forms are described in detail herein. In some or any embodiments, the unit dosage comprises 1 to 1000 mg, 1 to 100 mg or 10 to 50 mg active ingredient. In particular embodiments, the unit dosages comprise about 1, 5, 10, 25, 50, 100, 125, 250, 500 or 1000 mg active ingredient. Such unit dosages can be prepared according to techniques familiar to those of skill in the art.

[00286] In some or any embodiments, dosages of the second agents to be used in a combination therapy are provided herein. In some or any embodiments, dosages lower than those which have been or are currently being used to treat pain are used in the combination therapies provided herein. The recommended dosages of second agents can be obtained from the knowledge of those of skill in the art. For those second agents that are approved for clinical use, recommended dosages are described in, for example, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ; which are incorporated herein by reference in their entirety.

[00287] In various embodiments, the therapies (*e.g.*, a compound provided herein and the second agent) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart,

at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. In various embodiments, the therapies are administered no more than 24 hours apart or no more than 48 hours apart. In some or any embodiments, two or more therapies are administered within the same patient visit. In other embodiments, the compound provided herein and the second agent are administered concurrently.

[00288] In other embodiments, the compound provided herein and the second agent are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week part, at about 1 to 2 weeks apart, or more than 2 weeks apart.

[00289] In some or any embodiments, administration of the same agent may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[00290] In some or any embodiments, a compound provided herein and a second agent are administered to a patient, in some or any embodiments, a subject, such as a human, in a sequence and within a time interval such that the compound provided herein can act together with the other agent to provide an increased benefit than if they were administered otherwise. In some or any embodiments, the second active agent can be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In some or any embodiments, the compound provided herein and the second active agent exert their effect at times which overlap. Each second active agent can be administered separately, in any appropriate form and by any suitable route. In other embodiments, the compound provided herein is administered before, concurrently or after administration of the second active agent.

[00291] In some or any embodiments, the compound provided herein and the second agent are cyclically administered to a patient. Cycling therapy involves the administration of a first agent (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the

administration of a second agent and/or third agent (*e.g.*, a second and/or third prophylactic or therapeutic agent) for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00292] In some or any embodiments, the compound provided herein and the second active agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a compound provided herein and the second agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

[00293] In other embodiments, courses of treatment are administered concurrently to a patient, *i.e.*, individual doses of the second agent are administered separately yet within a time interval such that the compound provided herein can work together with the second active agent. In some or any embodiments, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

[00294] The second agent can act additively or synergistically with the compound provided herein. In some or any embodiments, the compound provided herein is administered concurrently with one or more second agents in the same pharmaceutical composition. In another embodiment, a compound provided herein is administered concurrently with one or more second agents in separate pharmaceutical compositions. In still another embodiment, a compound provided herein is administered prior to or subsequent to administration of a second agent. Also contemplated are administration of a compound provided herein and a second agent by the same or different routes of administration, *e.g.*, oral and parenteral. In some or any embodiments, when the compound provided herein is administered concurrently with a second agent that potentially produces adverse side effects including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

Kits

[00295] Also provided are kits for use in methods of treatment of pain and/or a condition associated with voltage-gated sodium channel function or a pain-related disorder. The kits can include a compound or composition provided herein, a second agent or composition, and instructions providing information to a health care provider regarding usage for treating the pain or a pain-related disorder. Instructions may be provided in printed form or in the form of an electronic medium such as a floppy disc, CD, or DVD, or in the form of a website address where such instructions may be obtained. A unit dose of a compound or composition provided herein, or a second agent or composition, can include a dosage such that when administered to a subject, a therapeutically or prophylactically effective plasma level of the compound or composition can be maintained in the subject for at least 1 day. In some or any embodiments, a compound or composition can be included as a sterile aqueous pharmaceutical composition or dry powder (*e.g.,* lyophilized) composition.

[00296] In some or any embodiments, suitable packaging is provided. As used herein, "packaging" includes a solid matrix or material customarily used in a system and capable of holding within fixed limits a compound provided herein and/or a second agent suitable for administration to a subject. Such materials include glass and plastic (*e.g.,* polyethylene, polypropylene, and polycarbonate) bottles, vials, paper, plastic, and plastic-foil laminated envelopes and the like. If e-beam sterilization techniques are employed, the packaging should have sufficiently low density to permit sterilization of the contents.

Methods of Use

[00297] Provided herein is a method for treating a condition associated with voltage-gated sodium channel function and/or pain in a subject, which comprises contacting the subject with a therapeutically or prophylactically effective amount of a compound of Formula (**I**), (**I-P1**), or (**I-P2**), including a single enantiomer, a mixture of an enantiomeric pair, an individual diastereomer, a mixture of diastereomers, an individual stereoisomer, a mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

[00298] Provided herein is a method for the treatment of a condition associated with voltage-gated sodium channel function in a subject, comprising the administration of a therapeutically or prophylactically effective amount of a compound of Formula (**I**), (**I-P1**), or (**I-P2**), described herein or a pharmaceutical composition described herein.

[00299] In some embodiments, the subject is a human. In a group of embodiments, the condition is pain or the condition is associated with pain. In some embodiments, the condition is pain. In some embodiments, the condition is associated with pain. In some embodiments, the pain is nociceptive pain. In some embodiments, the pain is neuropathic pain. In some embodiments, the pain is inflammatory pain. In some embodiments, the pain is refractory to other forms of pain medications.

[00300] In a group of embodiments, the condition is selected from the group consisting of erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal neuralgia, multiple sclerosis, osteoarthritis, postherpetic neuralgia, cancer pain, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, and postsurgical pain. In a group of embodiments, the condition is selected from the group consisting of epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotropic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

[00301] In some or any embodiments, provided herein are methods for treating pain and/or a condition associated with voltage-gated sodium channel function in a subject. In some or any embodiments, the methods encompass the step of administering to the subject in need thereof an amount of a compound effective for the treatment pain and/or a condition associated with voltage-gated sodium channel function in combination with a second agent effective for the treatment or prevention of pain and/or a condition associated with voltage-gated sodium channel function. The compound can be any compound as described herein, and the second agent can be any second agent described in the art or herein. In some or any embodiments, the compound is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

[00302] In some or any embodiments, provided herein are methods for treating a condition associated with voltage-gated sodium channel function in a subject. In some or any embodiments, the methods encompass the step of administering to the subject in need thereof a therapeutically or prophylactically effective amount of a compound effective for the treatment of a condition associated with voltage-gated sodium channel function in combination with a second agent effective for the treatment of a condition associated with voltage-gated sodium channel function. The compound can be any compound as described herein, and the second agent can be any second agent described in the art or herein. In some or any

embodiments, the compound is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

[00303] In some or any embodiments, provided herein is of inhibiting $NA_V1.8$ comprising contacting $NA_V1.8$ with a compound of Formula (**I**), (**I-P1**), (**I-P2**), and Compounds 1-51, 56, 59, 60, 82, 116, 119, and 169-206.

[00304] In some or any embodiments, provided herein is of inhibiting $NA_V1.8$ comprising contacting $NA_V1.8$ with a compound of Formula (**I**), (**I-P2**), and Compounds 1-127 and 169-206.

[00305] In some or any embodiments, provided herein is of inhibiting $NA_V1.8$ comprising contacting $NA_V1.8$ with a compound of Formula (**I**) and Compounds 1-206.

[00306] In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is associated with a condition or is a condition selected from acute pain, anal fissures, back pain, chronic pain, dental pain, joint pain, neck pain, neuropathic pain, obstetric pain, post-herpetic neuralgia, shingles, tension headaches, trigeminal blepharospasm, pain associated with cardiac arrythmia, focal dystonia, hyperhidrosis, muscle spasms, urinary bladder relaxation, visceral pain, sympathetically maintained pain, myositis pain, musculoskeletal pain, lower back pain, pain from sprains and strains, pain associated with functional bowel disorders, non-cardiac chest pain, pain associated with irritable bowel syndrome, pain associated with myocardial ischemia, toothache pain, pain from dysmenorrhea, erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal neuralgia, multiple sclerosis, osteoarthritis, postherpetic neuralgia, cancer, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, dry eye syndrome, (acute) corneal injuries or abrasions, corneal infections, pain associated with Parkinson's disease, pain associated with ALS, and surgery (in some embodiments, post-surgery; in some embodiments, ocular surgery). In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is pain in an acute care setting, including post-surgery. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is pain in an acute care setting, including post-surgery and the compound is administered intravenously. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is ocular pain. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is ocular pain and the compound is administered topically. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute or chronic

pain. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute or chronic pain and the compound is administered subcutaneously. In some or any embodiments, the pain to be reduced, ameliorated, treated, or prevented is subacute or chronic pain and the compound is administered orally.

[00307] In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from itch, cough, epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotrophic lateral sclerosis (ALS), cardiac arrhythmia, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder. In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from pain, itch, cough, glaucoma, and ischemia. In some or any embodiments, the condition associated with voltage-gated sodium channel function is selected from pain, itch, and cough. In some or any embodiments, the condition associated with voltage-gated sodium channel function is pain.

[00308] In some or any embodiments, the compounds described herein are used for delaying the onset of pain, or reducing the severity or duration of pain. In some or any embodiments, the compounds described herein are used for the reduction of the severity or duration of pain associated with voltage-gated sodium channel function. In some embodiments, the compounds described herein are used for delaying or preventing onset of pain.

[00309] In some or any embodiments, the compounds described herein are used for prevention of pain or of a condition associated with voltage-gated sodium channel function.

[00310] In some or any embodiments, the compounds described herein are used for treatment of pain or of a condition associated with voltage-gated sodium channel function.

Assay Methods

[00311] Compounds can be assayed for efficacy in treating pain and/or a condition associated with voltage-gated sodium channel function according to any assay known to those of skill in the art. Exemplary assay methods are provided elsewhere herein.

Second Therapeutic Agents

[00312] In some or any embodiments, the compounds and compositions provided herein are useful in methods of treatment of pain and/or a condition associated with voltage-gated sodium channel function, that comprise further administration of a second agent effective for the treatment of pain and/or a pain-related disorder and/or a condition associated with voltage-gated sodium channel function. The second agent can be any agent known to those of skill in the art to be effective for the treatment of pain and/or a pain-related disorder and/or a condition

associated with voltage-gated sodium channel function, including those currently approved by the United States Food and Drug Administration, or other similar body of a country foreign to the United States. In some or any embodiments, the second agent is a local anesthetic (in some or any embodiments, a steroid), an opioid, a vasoconstrictor, a glucocorticoid, adrenergic drugs (in some or any embodiments, alpha agonists or mixed central-peripheral alpha-2- agonists), vanilloids, an anti-inflammatory agent (*e.g.* NSAID, or an anti-inflammatory agent associated with ocular conditions, including cyclosporine and lifitegrast) or a chemical permeation enhancer. In some embodiments, the second agent is an inhibitor of Na_V 1.8. In some or any embodiments, chemical permeation enhancers include anionic surfactants, cationic surfactants, nonionic surfactants. In some or any embodiments, the second agent is bupivacaine, levobupivicaine, tetracaine, ropivacaine, epinephrine, phenylephrine, clonidine, sodium lauryl sulfate, sodium octyl sulfate, dodecyltrimethylammonium bromide, octyltrimethylammonium bromide, polyoxyethylene (20) sorbitan monolaurate, and/or polyoxyethylene (20) sorbitan monooleate.

[00313] In some or any embodiments, a compound provided herein is administered in combination with one second agent. In further embodiments, a compound provided herein is administered in combination with two second agents. In still further embodiments, a compound provided herein is administered in combination with two or more second agents.

[00314] As used herein, the term "in combination" includes the use of more than one therapy (e.*g.*, one or more prophylactic and/or therapeutic agents). The use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to a subject with a disorder.

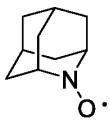
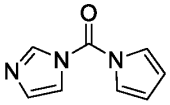
[00315] As used herein, the term "synergistic" includes a combination of a compound provided herein and another therapy (*e.g.*, a prophylactic or therapeutic agent) which has been

or is currently being used to prevent, manage or treat a disorder, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a disorder. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention or treatment of a disorder). In addition, a synergistic effect can result in improved efficacy of agents in the prevention or treatment of a disorder. Finally, a synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

[00316] The active compounds provided herein can be administered in combination or alternation with another therapeutic agent, in particular an agent effective in the treatment of pain and/or a pain-related disorder and/or a condition associated with voltage-gated sodium channel function. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the pain or a pain-related disorder to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

EXAMPLES

[00317] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); mM (millimolar); μM (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); hr or hrs (hours); min (minutes); MS (mass spectrometry); ESI (electrospray ionization); Ph (phenyl); TLC (thin layer

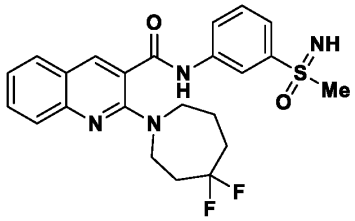
chromatography); HPLC (high pressure liquid chromatography); THF (tetrahydrofuran); $CDCl_3$ (deuterated chloroform); AcOH (acetic acid); DCM (dichloromethane); DMSO (dimethylsulfoxide); DMSO-d_6 (deuterated dimethylsulfoxide); EtOAc (ethyl acetate); MeOH (methanol); Tces (2,2,2-trichloroethoxysulfonyl); -Si(*tert*-Bu)$(Ph)_2$ and -Si^{t}BuPh$_2$ (tert-butyl-diphenylsilyl); and BOC (*t*-butyloxycarbonyl). AZADO refers to . CDI refers to .

[00318] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in ° C (degrees Celsius). All reactions are conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

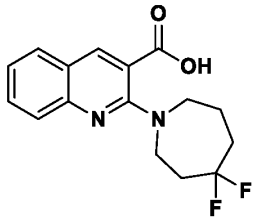
Synthetic Examples

Compound 1

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide

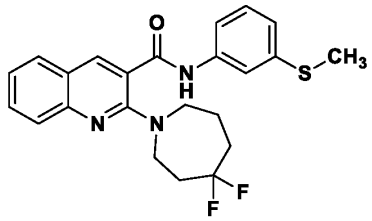


Synthesis of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid



[00319] To a mixture of 2-chloroquinoline-3-carboxylic acid (104 mg, 0.5 mmol) and 4,4-difluoroazepane hydrogen chloride (85.5 mg, 0.5 mmol) in N,N-dimethylformamide (5 mL), potassium carbonate (345 mg, 2.5 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography with a gradient of 0-100% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid as a yellow oil.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylthio)phenyl)quinoline-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide

[00320] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (18.5 mg, 0.06 mmol) in dichloromethane (2 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.344 mg, 0.09 mmol) and 4-dimethylaminopyridine (DMAP) (22.1 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 15 minutes. Then, 3-(methylthio)aniline (7.4 μL, 0.06 mmol) was added to the reaction mixture and stirred at room temperature for 18 hours. The progress of the reaction was monitored by LCMS. After the completion of reaction, dichloromethane was removed in vacuo and the resulting mixture was diluted with water and acetonitrile and purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford *2-(4,4-difluoroazepan-1-yl)-N-(3-(methylthio)phenyl)quinoline-3-carboxamide was a white powder.*

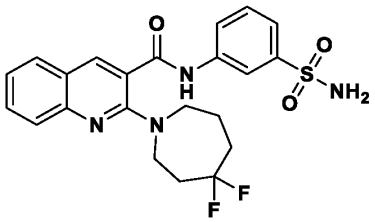
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide

[00321] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylthio)phenyl)quinoline-3-carboxamide (25.8 mg, 0.056 mmol) in MeOH (3 mL) was added ammonium carbonate (10.7 mg, 0.11 mmol) then (diacetoxyiodo)benzene (44.8 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 90 minutes. The progress of the reaction was monitored by LCMS. Methanol was removed in vacuo and the resulting crude mass was diluted with water and acetonitrile and purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 459.17, found: 458.8

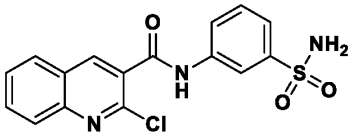
[00322] ^{1}H NMR (400 MHz, CD_3CN) δ 8.52 (s, 1H), 8.43 (s, 1H), 7.96 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.93 – 7.85 (m, 2H), 7.82 – 7.75 (m, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 3.91 – 3.83 (m, 2H), 3.73 (t, *J* = 5.8 Hz, 2H), 3.23 (s, 3H), 2.17 – 2.07 (m, 2H), 2.03 – 1.97 (m, 4H).

Compound 2

Synthesis of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide



Synthesis of 2-chloro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide



[00323] To a mixture of 2-chloroquinoline-3-carboxylic acid (52 mg, 0.25 mmol) and oxalyl chloride (39.4 μL, 0.45 mmol) in dichloromethane (2 mL) was added one drop of N,N-dimethylformamide. The reaction mixture was stirred for 15 minutes at room temperature. Then, a solution of 3-aminobenzenesulfonamide (43 mg, 0.25 mmol) and diisopropylethylamine (131 μL, 0.75 mmol) in dichloromethane (2 mL) and N,N-dimethylformamide (0.5 mL) was added to the stirred solution. The reaction mixture was stirred for 1 hour at room temperature. Dichloromethane was removed in vacuo and the crude

mixture was purified by silica gel column chromatography with a gradient of ethyl acetate and hexanes to afford 2-chloro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a yellow oil.

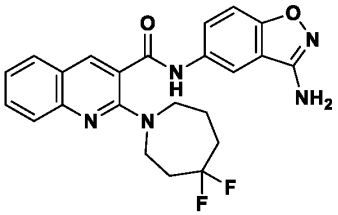
Synthesis of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00324] To a solution of 2-chloro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide (14 mg, 0.04 mmol) and 4,4-difluoroazepane hydrogen chloride (7 mg, 0.04 mmol) in *N,N*-dimethylformamide (1 mL), potassium carbonate (22 mg, 0.16 mmol) was added at room temperature. The reaction mixture was stirred at 70 °C for 16 hours then 80 °C for 18 hours. The progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with water and hydrochloric acid 1 N then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by reverse phase HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as white solid. LRMS (ESI): Calcd $[M+H]^+$: 461.15, found: 460.9.

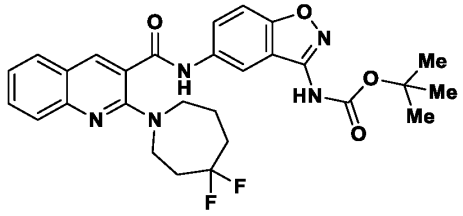
[00325] ^{1}H NMR (400 MHz, CD_3CN) δ 8.44 (s, 1H), 8.38 – 8.32 (m, 1H), 7.92 – 7.87 (m, 1H), 7.83 – 7.80 (m, 2H), 7.69 – 7.63 (m, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.00 – 6.93 (m, 1H), 3.87 – 3.79 (m, 2H), 3.72 – 3.65 (m, 2H), 2.49 – 2.40 (m, 4H), 2.15 – 2.06 (m, 2H).

Compound 3

Synthesis of N-(3-aminobenzo[d]isoxazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of tert-butyl (5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[d]isoxazol-3-yl)carbamate



[00326] To a mixture of 2-chloroquinoline-3-carboxylic acid (15 mg, 0.05 mmol) and oxalyl chloride (8 μL, 0.09 mmol) in dichloromethane (1 mL) was added one drop of N,N-dimethylformamide. The reaction mixture was stirred for 15 minutes at room temperature. Then, a solution of *tert*-butyl (5-aminobenzo[*d*]isoxazol-3-yl)carbamate (14 mg, 0.05 mmol) and diisopropylethylamine (26 μL, 0.15 mmol) in dichloromethane (1 mL) was added to the stirred solution. The reaction mixture was stirred for 18 hour at room temperature. Dichloromethane was removed in vacuo and the crude mixture was purified by reverse phase HPLC to afford *tert*-butyl (5-aminobenzo[*d*]isoxazol-3-yl)carbamate as white solid.

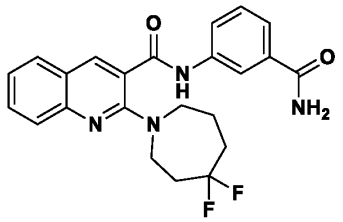
Synthesis of N-(3-aminobenzo[d]isoxazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00327] To a solution of *tert*-butyl (5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[*d*]isoxazol-3-yl)carbamate (26 mg, 0.05 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (300 μL). The reaction mixture was stirred for 2 hours then the volatiles were removed in vacuo. The crude mixture was purified with Combiflash using a gradient of 0 to 100% ethyl acetate in hexane to afford *tert*-butyl (5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[*d*]isoxazol-3-yl)carbamate as a light yellow oil. LRMS (ESI): Calcd $[M+H]^+$: 438.17, found: 437.9

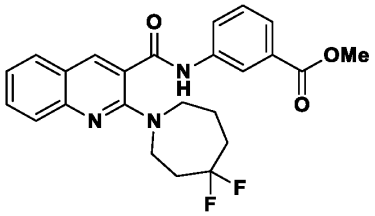
[00328] ^{1}H NMR (400 MHz, CD_3CN) δ 8.31 (s, 1H), 8.29 – 8.26 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.72 – 7.57 (m, 3H), 7.41 (d, J = 9.0 Hz, 1H), 7.37 – 7.28 (m, 1H), 3.84 – 3.76 (m, 2H), 3.65 (t, J = 6.0 Hz, 2H), 2.51 – 2.37 (m, 2H), 2.34 – 2.31 (m, 2H), 2.13 – 2.02 (m, 2H).

Compound 4

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzoate



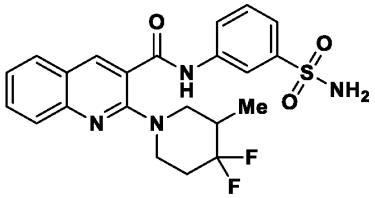
[00329] To a mixture of 2-chloroquinoline-3-carboxylic acid (15 mg, 0.05 mmol) and oxalyl chloride (8 μL, 0.09 mmol) in dichloromethane (1 mL) was added one drop of N,N-dimethylformamide. The reaction mixture was stirred for 15 minutes at room temperature. Then, a solution of 3-aminobenzamide (8 mg, 0.05 mmol) and diisopropylethylamine (26 μL, 0.15 mmol) in dichloromethane (1 mL) was added to the stirred solution. The reaction mixture was stirred for 18 hour at room temperature. Dichloromethane was removed in vacuo and the crude mixture was purified by reverse phase HPLC to afford methyl 3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzoate as white solid.

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00330] Methyl 3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzoate (19 mg, 4.3 mmol) was mixed with 7 N ammonia in methanol (5 mL) in a sealed vial at 50 °C for 18 hours. The volatiles were removed in vacuo and the crude mixture was purified by reverse phase HPLC to afford *N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide* as white solid. LRMS (ESI): Calcd $[M+H]^+$: 425.18, found: 424.9.

[00331] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.88 – 7.78 (m, 2H), 7.65 – 7.57 (m, 2H), 7.54 – 7.46 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.56 – 3.47 (m, 2H), 2.39 – 2.26 (m, 2H), 2.00 – 1.86 (m, 2H), 1.86 – 1.77 (m, 2H).

Compound 5



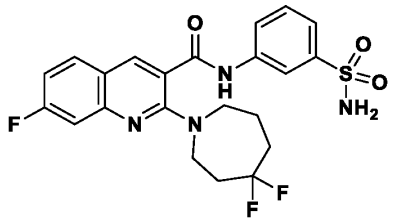
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00332] To a solution of 2-chloro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide (14 mg, 0.04 mmol) and 4,4-difluoro-3-methylpiperidine hydrogen chloride (7 mg, 0.04 mmol) in *N,N*-dimethylformamide (1 mL), potassium carbonate (22 mg, 0.16 mmol) was added at room temperature. The reaction mixture was stirred at 70 °C for 16 hours then 80 °C for 18 hours. The progress of the reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with water and hydrochloric acid 1N then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by reverse phase HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as white solid. LRMS (ESI): Calcd $[M+H]^+$: 461.15, found: 460.9.

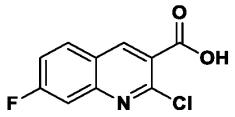
[00333] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.85 (s, 1H), 8.49 – 8.40 (m, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81 – 7.70 (m, 3H), 7.58 – 7.48 (m, 2H), 3.78 – 3.61 (m, 2H), 3.46 – 3.33 (m, 1H), 3.19 – 3.09 (m, 1H), 2.40 – 2.33 (m, 1H), 2.29 – 2.17 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H).

Compound 6

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

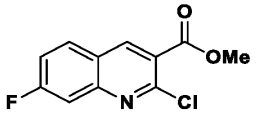


Synthesis of 2-chloro-7-fluoroquinoline-3-carboxylic acid



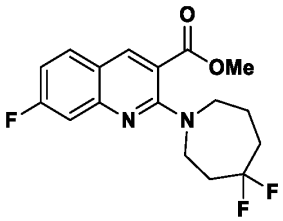
[00334] A stirred solution of 2-chloro-7-fluoroquinoline-3-carbaldehyde (1.0 g, 4.77 mmol) in ethanol (30 mL), silver nitrate (1.3 g, 7.63 mmol) was added. The reaction mixture was stirred for 1 hours at room temperature. Afterwards, a solution of sodium hydroxide (0.95 g, 23.9 mmol) in 80% aqueous ethanol was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, the reaction mixture was filtered through celite bed and solvent was removed by rotary evaporation and diluted with water, acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-chloro-7-fluoroquinoline-3-carboxylic acid as an off-white solid.

Synthesis of methyl 2-chloro-7-fluoroquinoline-3-carboxylate



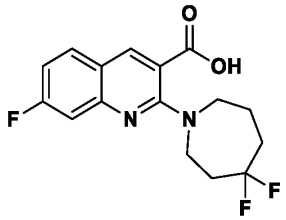
[00335] To a solution of 2-chloro-7-fluoroquinoline-3-carboxylic acid (0.9 g, 3.99 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (2.21 g, 12 mmol) and (0.60 ml, 9.97mmol) at room temperature and stirred for 12 hours at 50 °C. After completion of reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford methyl 2-chloro-7-fluoroquinoline-3-carboxylate as a light yellow solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylate



[00336] To a mixture of methyl 2-chloro-7-fluoroquinoline-3-carboxylate (550 mg, 2.3 mmol) and 4,4-difluoroazepane hydrogen chloride (0.59 g, 3.44 mmol) in *N,N*-dimethylformamide (5 mL), potassium carbonate (1.27 g, 12 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylate as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid



[00337] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylate (0.65 g, 1.92 mmol) in methanol (8 mL), tetrahydrofuran (8 mL) and water (8 mL) was added lithium hydroxide (0.162 g, 3.84 mmol). The reaction mixture was stirred at room temperature for 16 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, solvent was removed under rotatory and diluted with water, then acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was combined, dried with sodium sulfate, filtered and concentrated to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

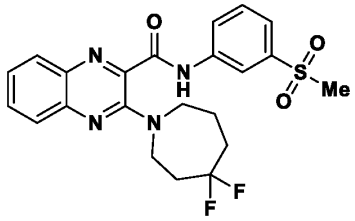
[00338] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.2 g, 0.62 mmol) in anhydrous dichloromethane (2 mL), was added oxalyl chloride (0.16 g, 1.2 mmol) and one drop of anhydrous *N,N*-dimethylformamide at 0 °C. The Reaction mixture was stirred at 0 °C for 30 minutes. The progress of reaction was monitored by TLC. After

completion, the reaction mixture was evaporated on vacuum under nitrogen atmosphere. The crude residue was dissolved into dry dichloromethane (6 mL) and added to the solution of 3-aminobenzene-1-sulfonamide (0.13 g, 0.74 mmol) and *N,N*-diisopropylethylamine (0.32 g, 2.5 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. After completion, the reaction mixture was diluted with dichloromethane and washed with water and brine solution. The combined organic layer was dried with sodium sulfate, filtered and concentrated to afford a crude product. The crude residue was purified by silica gel column chromatography with a gradient of 20-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 479.14, found: 479.21.

[00339] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.37 (s, 1H), 8.31 (s, 1H), 7.94 (t, J = 8 Hz, 1H), 7.86-7.84 (m, 1H), 7.58-7.56 (m, 2H), 7.42 (s, 2H), 7.34-7.31 (m, 1H), 7.23-7.18 (m, 1H), 4.04 (d, J = 3.2 Hz, 2H), 3.60 (t, J = 5.6 Hz, 2H), 2.40-2.35 (m, 2H), 2.06-1.98 (m, 2H), 1.90-1.88 (m, 2H).

Compound 7

Synthesis of 3-(4,4-difluoroazepan-1-yl)-N-(3-methanesulfonylphenyl)quinoxaline-2-carboxamide



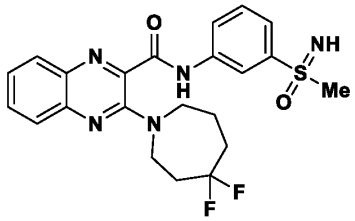
[00340] To a solution of 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid (0.2 g, 0.65 mmol) in *N,N*-dimethylformamide (5 mL) was added (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (0.37 g, 0.98 mmol) and *N,N*-diisopropylethylamine (0.57 mL, 3.25 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for 15 minutes. Afterwards, 3-methanesulfonylaniline (0.13 g, 0.78 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated under vacuum to obtain the crude product. The crude product was purified by flash column chromatography with a gradient of 40-50%

ethyl acetate in hexanes to afford 3-(4,4-difluoroazepan-1-yl)-*N*-(3-methanesulfonylphenyl)quinoxaline-2-carboxamide as a yellow solid. MS (ESI): Calcd $[M+H]^+$: 461.15, found: 461.20.

[00341] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 8.39 (s, 1H), 8.08-8.06 (m, 1H), 7.95-7.93 (d, J = 8 Hz, 1H), 7.72-7.67 (m, 4H), 7.52-7.48 (m, 1H), 3.80-3.78 (m, 2H), 3.67-3.64 (m, 2H), 3.24 (s, 3H), 2.55-2.32 (m, 2H), 2.04-2.02 (m, 2H), 1.93-1.92 (m, 2H).

Compound 8

3-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoxaline-2-carboxamide

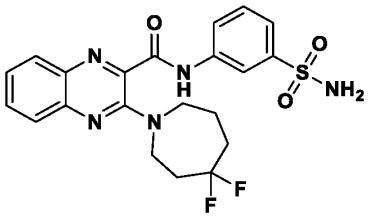


[00342] To a solution of 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid (0.35 g, 1.15 mmol) in *N,N*-dimethylformamide (5 mL) was added *N,N*-diisopropylethyl amine (0.77 g, 5.7 mmol) and (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluoro phosphate (0.65 g, 1.7 mmol) at 0 ^{0}C and stirred for 15 min at room temperature. Afterwards, (3-aminophenyl)(imino)methyl-λ^6-sulfanone (0.23 g, 1.4 mmol) was added and reaction mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to obtain the crude. The crude mass was purified by reverse phase HPLC to afford 3-(4,4-difluoroazepan-1-yl)-*N*-(3-(S-methylsulfonimidoyl) phenyl)quinoxaline-2-carboxamide as white solid. MS (ESI): Calcd $[M+H]^+$: 460.16, found: 460.25.

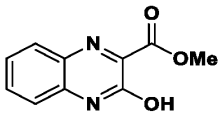
[00343] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.38 (s, 1H), 8.031 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 7.71 (d, J = 8 Hz, 3H), 7.65 (t, J = 8 Hz, 1H), 7.52-7.49 (m, 1H), 4.34 (s, 1H), 3.80.-3.78 (m, 2H), 3.67-3.64 (m, 2H), 3.085 (s, 3H), 2.40-2.37 (m, 2H), 2.07-1.99 (m, 2H), 1.89-1.88 (m, 2H).

Compound 9

Synthesis of 3-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide

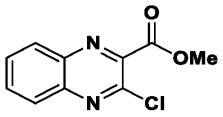


Synthesis of methyl 3-hydroxyquinoxaline-2-carboxylate



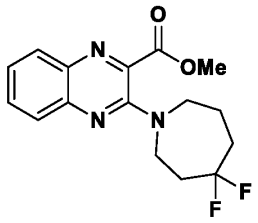
[00344] A stirred solution of 2-hydroxyquinoline-3-carboxylic acid (10 g, 52.6 mmol) in methanol (100 mL) was cooled to 0 °C. Then sulfuric acid (20 mL) was added dropwise. The reaction mixture was heated at 70 °C for 12 hours. The progress of the reaction was monitored by TLC. After completion, the methanol was removed under vacuum. The residue thus obtained was dissolved into ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material. The crude material was triturated with diethyl ether and pentane to afford the desire product methyl 3-hydroxyquinoxaline-2-carboxylate as a light orange solid.

Synthesis of methyl 3-chloroquinoxaline-2-carboxylate



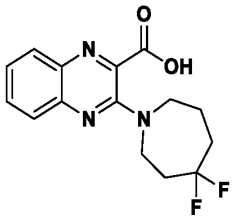
[00345] A mixture of methyl 3-hydroxyquinoxaline-2-carboxylate (5 g, 24.5 mmol) and phosphorus oxychloride (75 mL) was refluxed at 130 °C for 12 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was then cooled to room temperature and excess of phosphorus oxychloride distilled out. The residue thus obtained was dissolved into ethyl acetate and neutralized with sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material. The crude material was triturated with diethyl ether and pentane to afford the desire product methyl 3-chloroquinoxaline-2-carboxylate as a light brown solid.

Synthesis of methyl 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylate



[00346] To a solution of methyl 3-chloroquinoxaline-2-carboxylate (5 g, 22.5 mmol) in *N*,*N*-dimethylformamide (50 mL) was added 4,4-difluoroazepane hydrochloride (5.8 g, 33.7 mmol) and potassium carbonate (15.5 g, 112 mmol). The mixture was heated at 70 °C for 16 hours under N_2 atmosphere. The progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude residue which was purified by silica gel column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford the desired compound methyl 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylate as a brown solid.

Synthesis of 3-(4,4-Difluoroazepan-1-yl)quinoxaline-2-carboxylic acid



[00347] To a solution of methyl 3-(4,4-difluoroazepan-1-yl) quinoxaline-2-carboxylate (5 g, 15.6 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL), lithium hydroxide (1.5 g, 62 mmol) and water (20 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum and residue was diluted with water, acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude material which was purified by triturated with diethyl ether and pentane to afford 3-(4,4-difluoroazepan-1-yl) quinoxaline-2-carboxylic acid as a light brown solid.

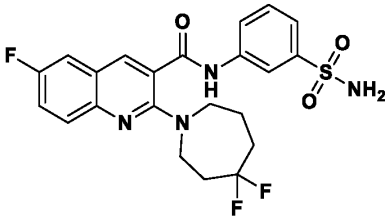
Synthesis of 3-(4,4-Difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide

[00348] To a solution of 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid (0.3 g, 0.9 mmol) in dichloromethane (6 mL) was added *N,N'*-dicyclohexylmethanediimine (0.24 mg, 1.17 mmol) and *N,N*-dimethylpyridin-4-amine (5.96 mg, 5 mol%) at 0 °C. Then 3-aminobenzene-1-sulfonamide (0.2 mg, 1.17 mmol) was added slowly and the resulting mixture was stirred at room temperature for overnight. After completion of reaction, the reaction mixture was passed through celite pad and filtrate was washed with brine water and dried over sodium sulfate and concentrated under reduced pressure to get crude material. The crude residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexanes to afford 3-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoxaline-2-carboxamide as yellow solid. MS (ESI): Calcd $[M+H]^+$: 462.14, found: 462.20

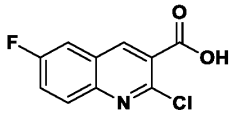
[00349] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 8.33 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.91-7.88 (m, 1H), 7.10 (d, J = 3.6 Hz, 2H), 7.61-7.59 (m, 2H), 7.52-7.48 (m, 1H), 7.43 (brs, 2H), 3.80-3.78 (m, 2H), 3.67 (t, J = 7.5 Hz, 2H), 2.44-2.40 (m, 2H), 2.09-2.04 (m, 2H), 1.99-1.92 (m, 2H).

Compound 10

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-fluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide



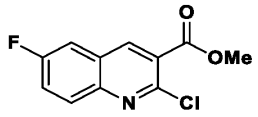
Synthesis of 2-chloro-6-fluoroquinoline-3-carboxylic acid



[00350] A stirred solution of 2-chloro-6-fluoroquinoline-3-carbaldehyde (=1 g, 4.8 mmol) in ethanol (30 mL), silver nitrate (1.3 g, 7.6 mmol) was added and the resulting reaction mixture was stirred for 1 hours at room temperature. Afterwards, to this, a solution of sodium hydroxide (0.96 g, 24 mmol) in 80% aqueous ethanol was added dropwise. The reaction mixture was

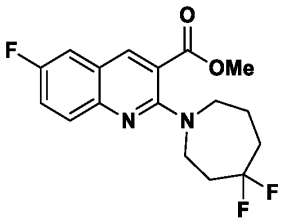
stirred at room temperature for 5 hours. After completi1on of reaction, the reaction mixture was filtered through celite and solvent was evaporated under rotary and diluted with water, acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-chloro-6-fluoroquinoline-3-carboxylic acid as an off-white solid.

Synthesis of methyl 2-chloro-6-fluoroquinoline-3-carboxylate



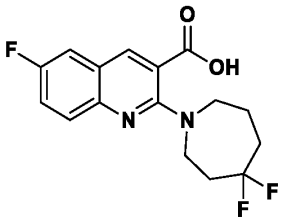
[00351] To a solution of 2-chloro-6-fluoroquinoline-3-carboxylic acid (0.75 g, 3.3 mmol) in *N,N*-dimethylformamide (7.5 mL) was added potassium carbonate (1.4 g, 10 mmol) and methyl iodide (0.5 ml, 8.3 mmol) at room temperature and stirred at 50 °C for 12 hours. After completion of reaction, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford methyl 2-chloro-6-fluoroquinoline-3-carboxylate as a light yellow solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6-fluoroquinoline-3-carboxylate



[00352] To s stirred solution of methyl 2-chloro-6-fluoroquinoline-3-carboxylate (0.55 g, 2.3 mmol) in *N,N*-dimethylformamide (5.5 mL), 4, 4-difluoroazepane hydrogen chloride (0.59 g, 3.45 mmol) and potassium carbonate (1.3 g, 9.2 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford the methyl 2-(4,4-difluoroazepan-1-yl)-6-fluoroquinoline-3-carboxylate as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-fluoroquinoline-3-carboxylic acid



[00353] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-6-fluoroquinoline-3-carboxylate (0.55 g, 1.6 mmol) in a mixture of methanol (5.5 mL), tetrahydrofuran (5.5 mL) and water (5.5 mL) (1:1:1) was added lithium hydroxide (0.14 g, 3.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, solvent was removed under rotatory and diluted with water, acidified with 1N hydrochloric solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-(4,4-difluoroazepan-1-yl)-6-fluoroquinoline-3-carboxylic acid as an off-white solid.

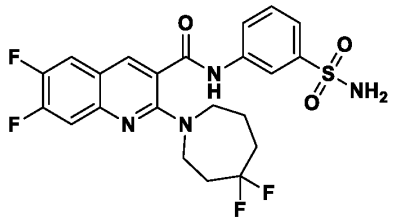
Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-fluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00354] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylic acid (0.4 g, 1.2 mmol) in dichloromethane (4 mL), oxalyl chloride (0.2 mL, 2.5 mmol) and one drop of *N,N*-dimethylformamide was added at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with dry dichloromethane (4 mL) and added to the mixture of 3-aminobenzenesulfonamide (0.25 g, 1.5 mmol) and *N,N*-diisopropyl ethyl amine (1.1 mL, 6.2 mmol) in dry dichloromethane (4 mL) at 0 °C and allowed to stirred at room temperature for 5 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 40-60% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6-fluoro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 479.14, found: 479.25.

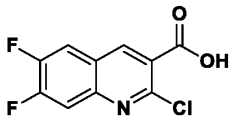
[00355] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (brs, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 7.86-7.83 (m, 1H), 7.70-7.67 (m, 1H), 7.67-7.65 (m, 1H), 7.58.751 (m, 3H), 7.43 (brs, 2H), 3.75-3.73 (m, 2H), 3.61-3.58 (t, J = 6.0 Hz, 2H), 2.54-2.38 (m, 2H), 2.07-1.96 (m, 2H), 1.89-1.88 (m, 2H).

Compound 11

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-difluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

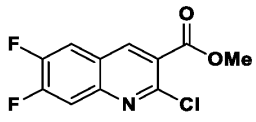


Synthesis of 2-chloro-6,7-difluoroquinoline-3-carboxylic acid



[00356] To a stirred solution of 2-chloro-6,7-difluoroquinoline-3-carbaldehyde (1 g, 4.4 mmol) in ethanol (50 mL) was added silver nitrate (1.1 g, 6.6 mmol) and reaction mixture was stirred for 30 min at room temperature. To this, a solution of sodium hydroxide (0.88 g, 22 mmol) in 80% aqueous ethanol was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered through Celite and solvent was evaporated by rotary and diluted with water and acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was combined, dried over sodium sulfate, filtered and concentrated to afford 2-chloro-6,7-difluoroquinoline-3-carboxylic acid as light yellow solid.

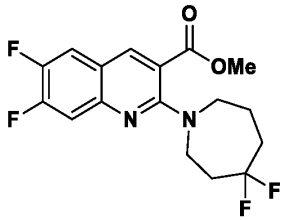
Synthesis of methyl 2-chloro-6,7-difluoroquinoline-3-carboxylate



[00357] To a stirred solution of 2-chloro-6,7-difluoroquinoline-3-carboxylic acid (1 g, 4.1 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (2.3 g, 16. mmol) and iodomethane (0.62 mL, 12.3 mmol). The reaction mixture was stirred for 12 hours at 50 °C. The progress of reaction was monitored by TLC. After completion of reaction, the reaction

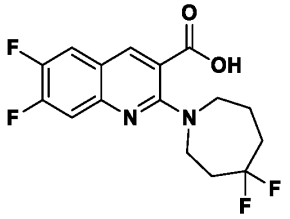
mixture was quenched with water and extracted with ethyl acetate. The organic layer was combined, dried with sodium sulfate, filtered and concentrated to afford methyl 2-chloro-6,7-difluoroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylate



[00358] To a solution of methyl 2-chloro-6,7-difluoroquinoline-3-carboxylate (1 g, 3.9 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (2.2 g, 15.5 mmol) and 4,4-difluoroazepane hydrogen chloride (1.0 g, 5.8 mmol). The resulting reaction mixture was heated to 70 ^{0} C and stirred for 16 hours. The progress of reaction was monitor by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was combined, dried over sodium sulfate, filtered and concentrated to afford the crude material. The crude material was purified by combi-flash with gradient 30-50% ethyl acetate in heptane to afford methyl 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylic acid



[00359] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylate (0.75 g, 2.1 mmol) in 1:1 methanol (5.48 mL) and tetrahydrofuran (5.48 mL) was added lithium hydroxide (0.18 g, 4.2 mmol). The reaction mixture was stirred 16 hours at room temperature. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was concentrated to remove solvent. The crude residue was diluted with water, acidified with 1 N hydrochloric acid solution and extracted with ethyl

acetate, dried over sodium sulfate and concentrated to afford 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylic acid as a yellow solid.

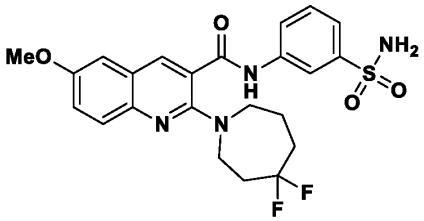
Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-difluoro-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00360] To a solution of 2-(4,4-difluoroazepan-1-yl)-6,7-difluoroquinoline-3-carboxylic acid (0.5 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) was added oxalyl chloride (0.25 mL, 2.9 mmol) and a drop of anhydrous *N,N*-dimethylformamide at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. After completion of reaction, the reaction mixture was evaporated in vacuum. The crude residue was redissolved into dry dichloromethane and added to the solution of 3-aminobenzene-1-sulfonamide (0.3 g, 1.75 mmol) and *N,N*-diisopropyl ethyl amine (0.76 g, 5.8 mmol) in dichloromethane (70 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 hour. After completion of reaction, the reaction mixture was diluted with dichloromethane and wash with water, brine solution. The combined organic layer was dried over sodium sulfate, filtered and concentrated to afford the crude product. The crude material was purified by using flash chromatography with gradient 20-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6,7-difluoro-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 497.13, found: 497.15.

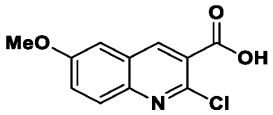
[00361] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.33 (s, 1H), 8.30 (s, 1H), 7.94 (t, J = 9.6 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.61 (s, 1H), 7.58 (d, J = 8 Hz, 2H), 7.42 (s, 2H), 3.74 (s, 2H), 3.60-3.58 (m, 2H), 2.40-2.37 (m, 2H), 2.07-1.99 (m, 2H), 1.89-1.88 (m, 2H).

Compound 12

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

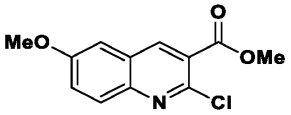


Synthesis of 2-chloro-6-methoxyquinoline-3-carboxylic acid



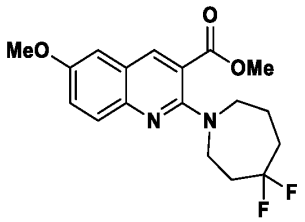
[00362] To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.4 g, 6.3 mmol) in ethanol (28 mL), silver nitrate (1.7 g, 10 mmol) was added and reaction mixture was stirred at room temperature for 1 hour. Afterwards, a solution of sodium hydroxide (1.3 g, 32 mmol) in 80% aqueous ethanol was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, the reaction mixture was filtered through celite and solvent was evaporated under rotary and diluted with water, acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-chloro-6-methoxyquinoline-3-carboxylic acid as an off-white solid.

Synthesis methyl 2-chloro-6-methoxyquinoline-3-carboxylate



[00363] To a solution of 2-chloro-6-methoxyquinoline-3-carboxylic acid (0.6 g, 2.5 mmol) in *N,N*-dimethylformamide (6 mL) was added potassium carbonate (1.0 g, 7.6 mmol) and methyl iodide (0.4 ml, 6.3 mmol) at room temperature and stirred for 12 hours at 50 °C. After completion of reaction, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure concentrated to afford methyl 2-chloro-6-methoxyquinoline-3-carboxylate as a light yellow solid.

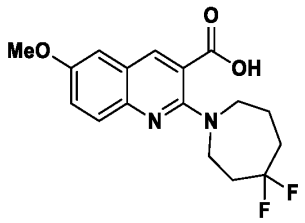
Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylate



[00364] To a stirred solution of methyl 2-chloro-6-methoxyquinoline-3-carboxylate (0.5 g, 2 mmol) in *N,N*-dimethylformamide (10 mL) was added 4, 4-difluoroazepane hydrogen

chloride (0.50 g, 3.0 mmol) and potassium carbonate (1 g, 8 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylate as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylic acid



[00365] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylate (0.45 g, 1.3 mmol) in a mixture of methanol (4.5 mL), tetrahydrofuran (4.5 mL) and water (4.5 mL) was added lithium hydroxide (0.11 g, 2.6 mmol) at room temperature and stirred for 16 hours. After completion of reaction, solvent was evaporated under rotary and diluted with water, acidified with 1 N hydrochloric solution and extracted with ethyl acetate. The organic layer was combined, dried over sodium sulfate, filtered and concentrated to afford 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylic acid as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

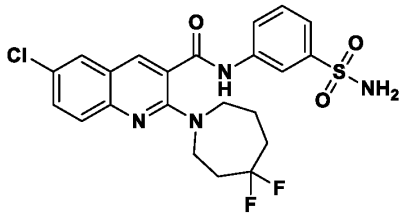
[00366] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-6-methoxyquinoline-3-carboxylic acid (0.24 g, 0.71 mmol) in dichloromethane (3 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.41 g, 1.1 mmol) and 4-dimethylaminopyridine (DMAP) (0.043 g, 0.36 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After completion of reaction, solvent was evaporated and diluted with acetonitrile (3 mL) and 3-aminobenzenesulfonamide (122 mg, 0.71 mmol) was added to the above solution and stirred at 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion

of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6-methoxy-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a yellow solid. MS (ESI): Calcd $[M+H]^+$: 491.16, found: 491.20.

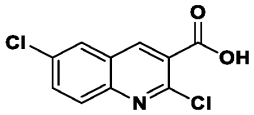
[00367] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 8.34 (brs, 1H), 8.24 (s, 1H), 7.86-7.83 (m, 1H), 7.60-7.54 (m, 3H), 7.42 (s, 2H), 7.32-7.30 (m, 2H), 3.25 (s, 3H), 3.72-3.70 (m, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.43-2.36 (m, 2H), 2.02-1.96 (m, 2H), 1.88-1.86 (m, 2H).

Compound 13

Synthesis of 6-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide



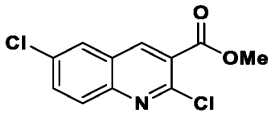
Synthesis of 2,6-dichloroquinoline-3-carboxylic acid



[00368] To a stirred solution of 2,6-dichloroquinoline-3-carbaldehyde (1.0 g, 4.4 mmol) in ethanol (30 mL) was added silver nitrate (1.2 g, 7.1 mmol) and reaction mixture was stirred for 1 hour at room temperature. Afterwards, a solution of sodium hydroxide (0.88 g, 22 mmol) in 80% aqueous ethanol was added drop wise and allowed to stirrer at room temperature for 5 hours. After completion of reaction, the reaction mixture was filtered through Celite and solvent was evaporated under rotary and diluted with water, acidified with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous

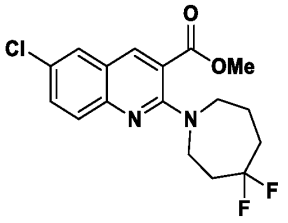
sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2,6-dichloroquinoline-3-carboxylic acid as an off-white solid.

Synthesis of methyl 2,6-dichloroquinoline-3-carboxylate



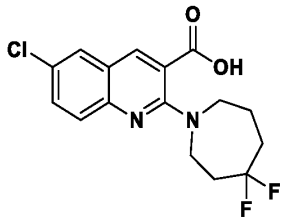
[00369] To a solution of 2,6-dichloroquinoline-3-carboxylic acid (0.9 g, 3.7 mmol) in *N,N*-dimethylformamide (9 mL) was added dipotassium carbonate (1.5 g, 11 mmol) and methyl iodide (0.6 ml, 9.3 mmol) at room temperature and stirred at 50 °C for 12 hours. After completion of reaction, reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford methyl 2,6-dichloroquinoline-3-carboxylate as a light yellow solid.

Synthesis of methyl 6-chloro-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxylate



[00370] To a stirred solution of methyl 2,6-dichloroquinoline-3-carboxylate (0.8 g, 3.1 mmol) in *N,N*-dimethylformamide (8 mL) was added 4, 4-difluoroazepane hydrogen chloride (0.63 g, 4.7 mmol) and potassium carbonate (1.7 g, 12.5 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford methyl 6-chloro-2-(4, 4-difluoroazepan-1-yl) quinoline-3-carboxylate as a yellow solid.

Synthesis of 6-chloro-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxylic acid



[00371] To a stirred solution of methyl 6-chloro-2-(4, 4-difluoroazepan-1-yl) quinoline-3-carboxylate (0.8 g, 2.3 mmol) in a mixture of methanol (8 mL), tetrahydrofuran (8 mL), and water (8 mL) was added lithium hydroxide (0.19 g, 4.5 mmol) and the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction, solvent was evaporated under rotatory and diluted with water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 6-chloro-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxylic acid as a yellow solid.

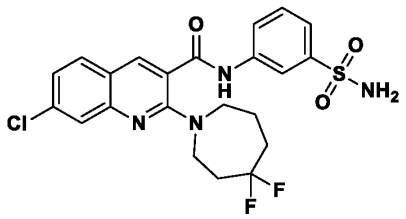
Synthesis of 6-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl) quinoline-3-carboxamide

[00372] To a stirred solution of 6-chloro-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxylic acid (0.33 g, 0.88 mmol) in dichloromethane (3 mL), was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.50 g, 1.3 mmol) and 4-dimethylaminopyridine (DMAP) (0.054 g, 0.44 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, solvent was evaporated in rotary and diluted with acetonitrile (3 mL) and to this, 3-aminobenzenesulfonamide (0.18 g, 1.1 mmol) was added and reflux for 16 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 6-chloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl) quinoline-3-carboxamide as a yellow solid. MS (ESI): Calcd $[M+H]^+$: 495.11, found: 495.20.

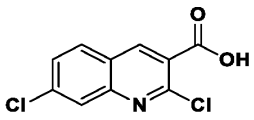
[00373] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.31 (d, J = 6.0 Hz, 2H), 7.95 (s, 1H), 7.85-7.83 (m, 1H), 7.65-7.62 (m, 2H), 7.60-7.55 (m, 2H), 7.42 (brs, 2H), 3.76-3.74 (m, 2H), 3.61 (t, J = 6.0 Hz, 2H), 2.40-2.38 (m, 2H), 2.06-1.99 (m, 2H), 1.96-1.88 (m, 2H).

Compound 14

Synthesis of 7-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

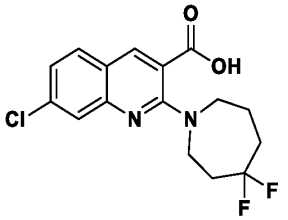


Synthesis of 2,7-dichloroquinoline-3-carboxylic acid



[00374] To a stirred solution of 2,7-dichloroquinoline-3-carbaldehyde (1.0 g, 4.4 mmol) in ethanol (20 mL) was added silver nitrate (1.2 g, 7.1 mmol). To this mixture, a solution of sodium hydroxide (0.9 g, 22 mmol) in water (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, the reaction mixture was filtered through a Celite pad and solvent was removed under rotatory evaporation to obtain crude mixture. The crude mixture was diluted with water and acidified with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material. The crude material was triturated with diethyl ether and pentane to afford 2,7-dichloroquinoline-3-carboxylic acid as an off-white solid.

Synthesis of 7-Chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid



[00375] To a solution of 2,7-dichloroquinoline-3-carboxylic acid (0.65 g, 2.7 mmol) in *N,N*-dimethylformamide (20 mL) was added 4,4-difluoroazepane hydrogen chloride (0.67 g, 34 mmol) and potassium carbonate (1.5 g, 11 mmol). The mixture was heated at 70 °C for 12 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion, the crude material was diluted with water followed by treatment with 1N hydrochloric acid solution to pH 6.0 and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was triturated with diethyl ether and pentane to afford the product 7-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid as light brown solid.

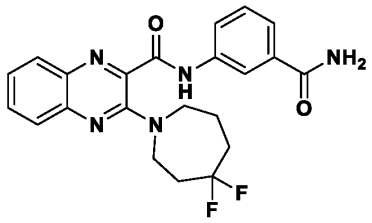
Synthesis of 7-Chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00376] To a solution of 7-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.30 g, 0.90 mmol) in dichloromethane (6 mL) was added oxalyl chloride (0.15 g, 1.0 mmol) under nitrogen atmosphere followed by 1-2 drops of *N,N*-dimethylformamide at 0 °C and continue the reaction for 1 hour at room temperature. After completion of reaction, solvent was removed under nitrogen atmosphere. The crude mixture was dissolved into dichloromethane (6 mL) and added to the solution of 3-aminobenzene-1-sulfonamide (0.18 g, 1.2 mmol) and *N,N*-diisopropylethyl amine (0.4 mL, 4.5 mmol) in dichloromethane (6 mL) solution at 0 °C and stirred the mixture for additional 1 hour at room temperature. The progress of reaction was monitor by TLC. After completion of reaction, the mixture was quenched with water then extracted with dichloromethane. The organic layer was combined, dried over sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 7-chloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as light brown solid. MS (ESI): Calcd $[M+H]^+$: 495.11, found: 495.15.

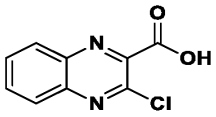
[00377] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.37 (s, 1H), 8.30 (s, 1H), 7.88-7.83 (m, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.58-7.54 (m, 2H), 7.42 (s, 2H), 7.32 (dd, J = 2.4, 8.8 Hz, 1H), 3.77-3.74 (m, 2H), 3.60 (t, J = 5.6 Hz, 2H), 2.44-2.37 (m, 2H), 2.00-1.99 (m, 2H), 1.95-1.88 (m, 2H).

Compound 15

Synthesis of N-(3-carbamoylphenyl)-3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxamide

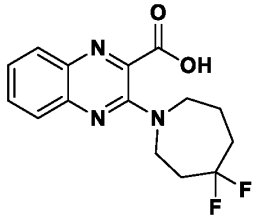


Synthesis of 3-chloroquinoxaline-2-carboxylic acid



[00378] A mixture of 3-hydroxyquinoxaline-2-carboxylic acid (2 g, 9.6 mmol) and phosphorous oxychloride (20 mL) was slowly heated to 120 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with ice-cold water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and resultant crude residue was triturated with *n*-pentane and diethyl ether to afford 3-chloroquinoxaline-2-carboxylic acid as a yellow solid.

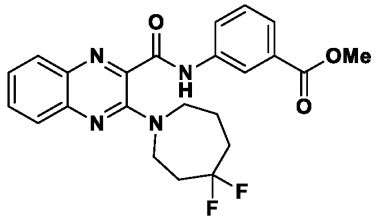
Synthesis of 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid



[00379] To a solution of 3-chloroquinoxaline-2-carboxylic acid (1.0 g, 1.65 mmol) in *N*,*N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrogen chloride (0.43 g, 2.5 mmol) and potassium carbonate (0.9 g, 6.6 mmol) at room temperature. The reaction mixture was heated at 78 ℃ for 12 hours. After completion of reaction, the crude material was diluted with cold-water followed by treatment with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in

hexanes to afford the desired compound 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid as a yellow solid.

Synthesis of methyl 3-(3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxamido)benzoate



[00380] To a solution of 3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxylic acid (0.4 g, 1.4 mmol) in dichloromethane (10 mL) was added oxalyl chloride (0.15 g, 2.7 mmol) and a drop of *N,N*-dimethylformamide at 0 °C under nitrogen atmosphere and stirred for 1 hour at room temperature. After completion of reaction, solvent was distilled out under nitrogen atmosphere. The crude mixture was dissolved into dichloromethane (10 mL) and added to the solution of 3-aminomethylbenzoate (0.29 g, 1.7 mmol) and *N,N*-diisopropylethylamine (0.40 mL, 4.5 mmol) in dichloromethane (10 mL) at 0 °C and stirred the mixture for 12 hours at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was quenched with water, extracted with dichloromethane. The combined organic layer was dried over sodium sulfate, filtered and concentrated to afford crude residue which was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford methyl 3-(3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxamido)benzoate as yellow solid.

Synthesis of N-(3-carbamoylphenyl)-3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxamide

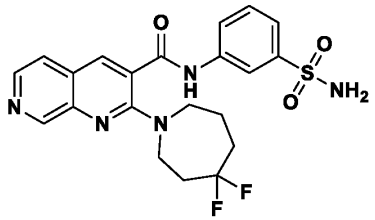
[00381] To a stirred solution of methyl 3-(3-(4,4-difluoroazepan-1-yl)quinoxaline-2-carboxamido)benzoate (0.28 g, 0.75 mmol) in ammonia solution (7 N ammonia in methanol, 10 mL) was added at room temperature. The reaction mixture was stirred at 100 °C in an autoclave for 28 hours. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed in vacuo. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes

to afford *N*-(3-carbamoylphenyl)-3-(4,4-difluoroazepan-1-yl) quinoxaline-2-carboxamide as yellow solid. MS (ESI): Calcd $[M+H]^+$: 426.17, found: 426.20.

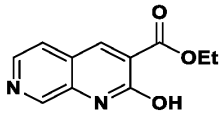
[00382] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 8.21 (t, J = 16.0 Hz, 1H), 7.95 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 8 Hz, 1.6 Hz, 1H), 7.70-7.71 (m, 2H), 7.64 (d, J = 8 Hz, 1H), 7.45-7.52 (m, 2H), 7.40 (s, 1H), 3.79-3.81 (m, 2H), 3.68 (t, J = 6Hz, 2H), 2.34-2.43(m, 2H), 2.03-2.08 (m, 2H), 1.91-1.99 (m, 2H)

Compound 16

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,7-naphthyridine-3-carboxamide

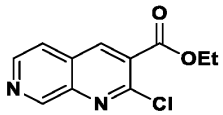


Synthesis of ethyl 2-hydroxy-1,7-naphthyridine-3-carboxylate



[00383] To a stirred solution of 3-aminoisonicotinaldehyde (2.5 g, 20.4 mmol) in ethanol (25 mL) was added diethyl malonate (9.4 mL, 61.5 mmol) and piperidine (0.65 mL, 6.2 mmol). The reaction mixture was refluxed and stirred for 18 hours. After completion of reaction, the reaction mixture was concentrated under reduced pressure to afford the crude material which was triturated with diethyl ether and pentane to furnish ethyl 2-hydroxy-1,7-naphthyridine-3-carboxylate as a yellow solid.

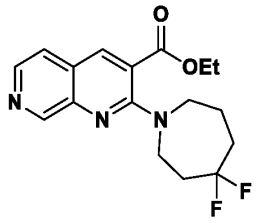
Synthesis of ethyl 2-chloro-1,7-naphthyridine-3-carboxylate



[00384] A mixture of ethyl 2-hydroxy-1,7-naphthyridine-3-carboxylate (2.8 g, 12.8 mmol) and phosphorus oxychloride (14 mL) was heated at 130 °C for 3 hours. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with cold water and basified with aq.

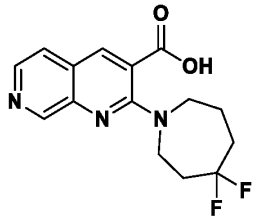
sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure to afford crude material. The crude residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford ethyl 2-chloro-1,7-naphthyridine-3-carboxylate as a yellow solid.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylate



[00385] To a stirred solution of ethyl 2-chloro-1,7-naphthyridine-3-carboxylate (1.0 g, 4.2 mmol) in *N*,*N*-dimethylformamide (10 mL), 4, 4-difluoroazepane hydrogen chloride (1.0 g, 6.4 mmol) and dipotassium carbonate (2.3 g, 17 mmol) was added at room temperature and slowly heated to 70 °C and stirred for 12 hours. After completion of reaction, the reaction mixture was cool to room temperature, diluted with ice cold water and extracted with ethyl acetate. The organic layer was combined, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford ethyl 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylate as a light yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid



[00386] To a stirred solution of ethyl 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylate (0.8 g, 2.4 mmol) in a mixture of methanol (8 mL), tetrahydrofuran (8 mL), and water (8 mL) was added lithium hydroxide (0.7 g, 4.8 mmol). The reaction mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated under rotary evaporation and diluted with

water, acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was combined, dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo to afford the crude material. The crude material was triturated with diethyl ether and pentane to afford 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid as a yellow solid.

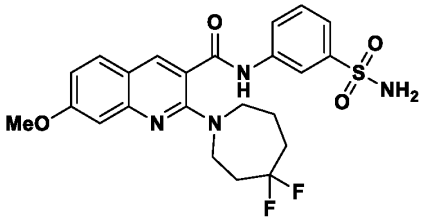
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,7-naphthyridine-3-carboxamide

[00387] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid (0.4 g, 1.3 mmol) in dichloromethane (4 mL), (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.74 g, 2 mmol) and 4-dimethylaminopyridine (DMAP) (0.08 g, 0.65 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction, solvent was evaporated under rotary and residue was diluted with acetonitrile (4 mL) and to this solution, 3-aminobenzenesulfonamide (0.27 g, 1.6 mmol) was added in one portion. The reaction mixture was heated to 70 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-1,7-naphthyridine-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 462.14, found: 462.20

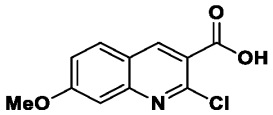
[00388] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 9.01 (s, 1H), 8.40 (s, 1H), 8.35 (d, J = 6.5 Hz, 1H), 8.30 (brs, 1H), 7.87-7.84 (m, 1H), 7.73 (d, J = 6.5 Hz, 1H), 7.60-7.56 (m, 2H), 7.43 (brs, 2H), 3.80-3.78 (m, 2H), 3.64 (t, J = 6.0 Hz, 2H), 2.42-2.39 (m, 2H), 2.07-1.98 (m, 2H), 1.92-1.90 (m, 2H)

Compound 17

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

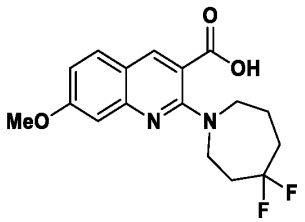


Synthesis of 2-chloro-7-methoxyquinoline-3-carboxylic acid **(2)**



[00389] To a stirred solution of 2-chloro-7-methoxyquinoline-3-carbaldehyde (2.0 g, 9.0 mmol) in ethanol (40 mL) was added silver nitrate (2.45 g, 14.4 mmol). To this mixture, a solution of sodium hydroxide (1.8 g, 45 mmol) in water (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, the reaction mixture was filtered through Celite and concentrated in vacuo to obtain the crude mixture. The crude mixture was diluted with water and acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to afford the crude material which purified by was trituration with diethyl ether and n-pentane to afford 2-chloro-7-methoxyquinoline-3-carboxylic acid as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-methoxyquinoline-3-carboxylic acid



[00390] To a solution of 2-chloro-7-methoxyquinoline-3-carboxylic acid (1.0 g, 4.2 mmol) in *N*,*N*-dimethylformamide (20 mL) was added 4,4-difluoroazepane hydrogen chloride (0.85 g, 6.3 mmol) and potassium carbonate (2.3 g, 16.8 mmol). The mixture was heated at 70 °C for 12 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After

completion of reaction, the crude material was diluted with cold water followed by treatment with 1N hydrochloric acid solution to pH 3~4.0 and extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude material which was purified by trituration with diethyl ether and n-pentane to afford 2-(4,4-difluoroazepan-1-yl)-7-methoxyquinoline-3-carboxylic acid as a light brown solid.

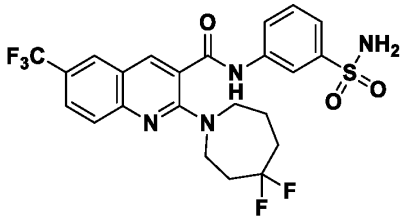
Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00391] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-methoxyquinoline-3-carboxylic acid (0.2 g, 0.6 mmol) in dichloromethane (4 mL) was added bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.34 g, 0.9 mmol) and *N*,*N*-dimethylpyridin-4-amine (DMAP) (0.037 g, 0.30 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, solvent was removed under rotatory and diluted with acetonitrile (4 mL) and added to the solution of 3-aminobenzenesulfonamide (0.1 g, 0.7 mmol) at room temperature. The reaction mixture was reflux for 18 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-7-methoxy-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as white solid. MS (ESI): Calcd $[M+H]^+$: 491.16, found: 491.20.

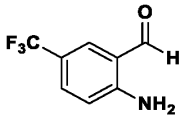
[00392] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.56 (s, 1H), 7.55 (d, J = 8 Hz, 1H), 7.40 (s, 2H), 7.02 (d, J = 4 Hz, 1H), 7.95 (dd, J = 2.4 Hz, J = 8 Hz, 1H), 3.88 (s, 3H), 3.74-3.73 (m, 2H), 3.59 (t, J = 8 Hz, 2H), 2.41-2.38 (m, 2H), 2.00-1.98 (m, 2H), 1.89-1.88 (m, 2H).

Compound 18

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)quinoline-3-carboxamide

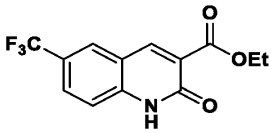


Synthesis of 2-amino-5-(trifluoromethyl)benzaldehyde



[00393] To a solution of 2-nitro-5-(trifluoromethyl)benzaldehyde (1.0 g, 4.5 mmol) in ethanol (10 mL) was added iron powder (2.5 g, 45 mmol) and hydrochloric acid (0.2 mL). The mixture was heated and stirred at 80 °C for 2 hours. After reaction completion, the reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved with ethyl acetate and washed with a saturated solution of sodium bicarbonate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-amino-5-(trifluoromethyl)benzaldehyde as a brown solid.

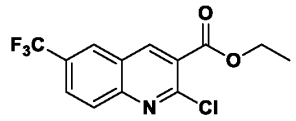
Synthesis of ethyl 2-oxo-6-(trifluoromethyl)-1,2-dihydroquinoline-3-carboxylate



[00394] To a solution of 2-amino-5-(trifluoromethyl)benzaldehyde (0.80 g, 4.2 mmol) in ethanol (10 mL) was added diethyl malonate (6.7 g, 42 mmol) and piperidine (1.4 g, 16.8 mmol). The mixture was heated at 80 °C for 5 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved in ethyl acetate and washed with brine. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash chromatography with a gradient of 70-80% ethyl acetate in

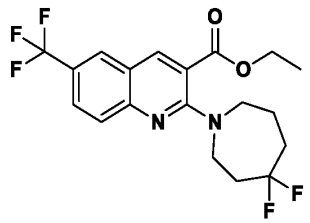
hexane to afford ethyl 2-oxo-6-(trifluoromethyl)-1,2-dihydroquinoline-3-carboxylate as a brown solid.

Synthesis of ethyl 2-chloro-6-(trifluoromethyl)quinoline-3-carboxylate



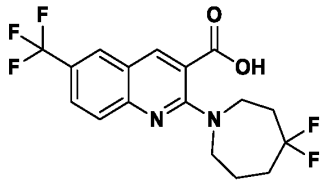
[00395] A solution of phosphorus oxychloride (5 mL) and ethyl 2-oxo-6-(trifluoromethyl)-1,2-dihydroquinoline-3-carboxylate (0.5 g, 1.7 mmol) was heated at 110 °C for 12 hours. After reaction completion, excess phosphorus oxychloride was distilled out and the residue was diluted with ice-cold water, neutralized with saturated solution of sodium bicarbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford ethyl 2-chloro-6-(trifluoromethyl)quinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylate



[00396] To a stirred solution of ethyl 2-chloro-6-(trifluoromethyl)quinoline-3-carboxylate (0.43 g, 1.4 mmol) in *N,N*-dimethylformamide (3 mL), 4,4-difluoroazepane hydrochloride (0.36 g, 2.1 mmol) and potassium carbonate (0.77 g, 5.6 mmol) were added. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford ethyl 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylate as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylic acid



[00397] To a stirred solution of ethyl 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylate (0.35 g, 0.87 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL), an aqueous solution of lithium hydroxide (0.14 g, 3.48 mmol) in water (1 mL) was added at room temperature and stirred for 12 hours. After reaction completion, the solvent was removed under reduced pressure and the residue was diluted with water, acidified with hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylic acid as a brown solid.

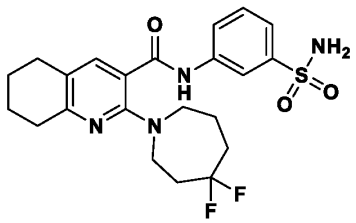
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)quinoline-3-carboxamide

[00398] To a solution of 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylic acid (0.25 g, 0.66 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.12 mL, 1.3 mmol) under nitrogen atmosphere followed by the addition of 2 drops of *N*,*N*-dimethylformamide at 0 °C. Then solution was warmed to room temperature and stirred for 1 hour. After reaction completion, the solvent was removed under nitrogen atmosphere. The residue was taken up in dichloromethane (6 mL) and added to a solution of 3-aminobenzenesulfonamide (0.09 g, 0.8 mmol) and *N*,*N*-diisopropylethylamine (0.6 mL, 3.3 mmol) in dichloromethane (5 mL) at 0 °C and stirred for additional 2 hours at room temperature. After reaction completion, the mixture was quenched with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-6-(trifluoromethyl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.035 g, 10%; LRMS (ESI): Calcd $[M+H]^+$: 529.13, found: 529.25.

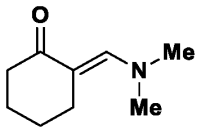
[00399] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.49 (d, J = 6.8 Hz, 1H), 8.30 (s, 2H),7.87-7.83 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.42 (s, 2H), 3.97-3.74 (m, 2H), 3.59 (t, J = 6.8 Hz, 2H), 2.45-2.37 (m, 2H), 2.01-1.96 (m, 2H), 1.91-1.90 (m, 2H).

Compound 19

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

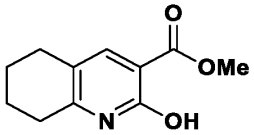


Synthesis of (E)-2-((dimethylamino)methylene)cyclohexan-1-one



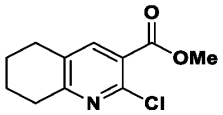
[00400] A mixture of cyclohexanone (10.0 g, 100 mmol) and 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (18 g, 100 mmol) was stirred at room temperature overnight. Afterwards, heated the reaction mixture at 110 °C for 12 hours. The progress of reaction was monitored by TLC and LCMS. After completion, the solvent was removed under rotatory evaporation to obtain crude (*E*)-2-((dimethylamino)methylene)cyclohexan-1-one as a brown liquid which was used as such into next step without any purification.

Synthesis of methyl 2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate



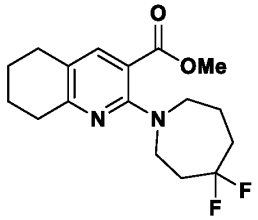
[00401] To the crude (*E*)-2-((dimethylamino)methylene)cyclohexan-1-one (15.0 g, 98 mmol) in methanol (75 mL) was added methyl 2-cyanoacetate (11 g, 107 mmol) and the reaction mixture was heated at 80 °C for 12 hours. After completion of reaction, the solvent was removed under rotatory evaporation and the crude mass which was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to afford methyl 2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate as white solid.

Synthesis of methyl 2-chloro-5,6,7,8-tetrahydroquinoline-3-carboxylate



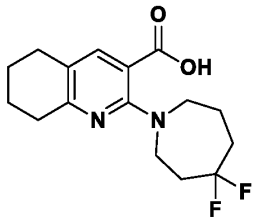
[00402] Methyl 2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate (3.3 g, 15 mmol) was dissolved into phosphorus oxychloride (33 mL) at room temperature and slowly heated to reflux for 12 hours. The reaction mixture was then cooled to room temperature and excess of phosphorus oxychloride was distilled out in vacuo. The residue obtained was dissolved into ethyl acetate and washed with aq. sodium bicarbonate solution. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate and concentrated in vacuum to afford the crude material. The crude material was triturated with diethyl ether and pentane to afford methyl 2-chloro-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00403] To a solution of methyl 2-chloro-5,6,7,8-tetrahydroquinoline-3-carboxylate (3.0 g, 13 mmol) in *N*,*N*-dimethylformamide (30 mL) was added 4,4-difluoroazepane hydrogen chloride (2.7 g, 15.6 mmol) and potassium carbonate (7.3 g, 5.2 mmol). The reaction mixture was heated at 100 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00404] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylate (1.5 g, 4.6 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was added lithium hydroxide (0.97 g, 20 mmol) in water (20 mL) and stirred at room temperature for 12 h. After completion of reaction, solvent was removed under rotatory evaporation and diluted with water, acidified with 1N hydrochloric solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

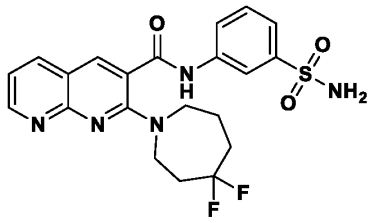
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00405] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.31 g, 1 mmol) in dichloromethane (10 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium3-oxide hexafluorophosphate (HATU) (0.57 g, 1.5 mmol) and 4-(dimethylamino)pyridine (0.006 g, 0.05 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with acetonitrile and to this solution, 3-aminobenzenesulfonamide (0.18 g, 1.1 mmol) was added and the mixture was heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, acetonitrile was removed under rotatory evaporation. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid. MS (ESI): Calcd $[M+H]^+$: 465.18, found: 465.25.

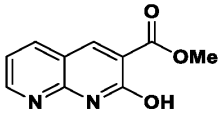
[00406] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.29 (s, 1H), 7.8 (d, J = 3.6 Hz, 1H), 7.52-7.51 (m, 2H), 7.42 (s, 1H), 7.37 (s, 2H), 3.57-3.56 (m, 2H), 3.38 (t, J = 5.6 Hz, 2H), 2.70-2.67 (m, 2H), 2.65-2.63 (m, 2H), 2.32-2.29 (m, 2H), 1.94-1.90 (m, 2H), 1.80-1.79 (m, 4H), 1.73-1.72 (m, 2H).

Compound 20

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,8-naphthyridine-3-carboxamide

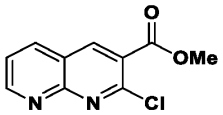


Synthesis of methyl 2-hydroxy-1,8-naphthyridine-3-carboxylate



[00407] To a stirred solution of 2-hydroxy-1,8-naphthyridine-3-carboxylic acid (5.0 g, 26 mmol) in methanol (50 mL), thionyl chloride (50 ml) was added dropwise at 0 °C under nitrogen atmosphere. After addition of thionyl chloride, the reaction mixture was slowly warmed to room temperature and then heated at 70 °C for 16 hours. After completion of reaction, the reaction mixture was cooled to room temperature, the solid precipitate formed was filtered and washed with water and dried under vacuum to afford methyl 2-hydroxy-1,8-naphthyridine-3-carboxylate as an off-white solid.

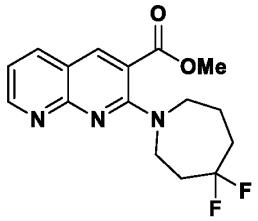
Synthesis of methyl 2-chloro-1,8-naphthyridine-3-carboxylate



[00408] A solution of methyl 2-hydroxy-1,8-naphthyridine-3-carboxylate (4.5 g, 22 mmol) in phosphorus oxychloride (50 mL) was heated at 130 °C for 16 hours under nitrogen atmosphere. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure and the crude residue was poured into crushed ice and basified with aqueous sodium bicarbonate and then extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate

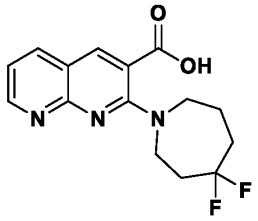
and evaporated under reduced pressure to obtain the crude product. The crude material was purified by flash column chromatography with a gradient of 50% ethyl acetate in hexanes to afford methyl 2-chloro-1,8-naphthyridine-3-carboxylate as a yellow oil.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylate



[00409] To a stirred solution of methyl 2-chloro-1,8-naphthyridine-3-carboxylate (1.2 g, 5.4 mmol) in *N,N*-dimethylformamide (12 mL), 4,4-difluoroazepane hydrochloride (1.4 g, 8.1 mmol) and potassium carbonate (3 g, 21.6 mmol) were added at room temperature. The resulting mixture was heated at 100 °C for 16 hours. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product. The crude product was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in heptane to afford methyl 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylate as a light yellow oil.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid



[00410] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylate (1.2 g, 3.7 mmol) in methanol (20 mL) and tetrahydrofuran (20 mL), aqueous solution of lithium hydroxide (0.36 g, 15 mmol) in water (20 mL) was added and the resulting reaction mixture was stirred at room temperature for 24 hours. Progress of the reaction was monitored by TLC. The organic solvents were removed under reduced pressure and diluted with water (50 mL), acidified with hydrochloric acid 1N and extracted with 20% isopropyl alcohol in chloroform. The organic layer was washed with brine, dried over anhydrous sodium

sulfate and evaporated under reduced pressure. The crude material was purified through trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid as a white solid.

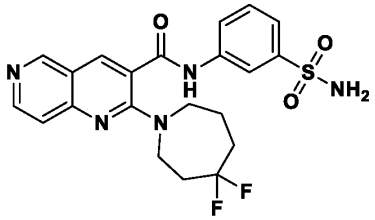
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,8-naphthyridine-3-carboxamide

[00411] To a stirred suspension of 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid (0.2 g, 0.65 mmol) in dry dichloromethane (20 mL), [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (0.37 g, 0.98 mmol) and *N,N*-dimethylpyridin-4-amine (0.039 g, 0.3 mmol) were added sequentially at 0 °C. The resulting mixture was stirred at room temperature for 18 hours. Then, the reaction mixture was evaporated under vacuum to remove the dichloromethane and the resulting residue was dissolved in acetonitrile (10 mL). To the resulting mixture, 3-aminobenzene-1-sulfonamide (0.13 g, 0.78 mmol) was added and reaction mixture was heated at 80 °C for 18 hours. After completion of reaction, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude. The crude product was purified by flash column chromatography with a gradient of 100% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-1,8-naphthyridine-3-carboxamide as a light yellow solid. MS (ESI): Calcd $[M+H]^+$: 462.14, found: 462.30.

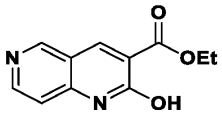
[00412] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.84-8.83 (m, 1H), 8.41 (s, 1H), 8.30-8.26 (m, 2H), 7.86-7.84 (m, 1H), 7.58-7.57 (m, 2H), 7.42 (s, 2H), 7.33-7.30 (m, 1H), 3.82-3.80 (m, 2H), 3.63-3.62 (m, 2H), 2.15-2.01 (m, 3H), 1.92-1.90 (m, 3H).

Compound 21

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,6-naphthyridine-3- carboxamide

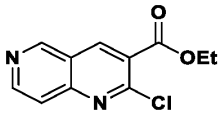


Synthesis of ethyl 2-hydroxy-1,6-naphthyridine-3-carboxylate



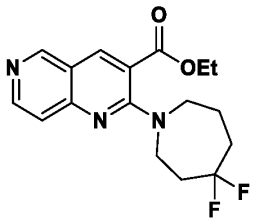
[00413] To a stirred solution of 4-aminonicotinaldehyde (5 g, 41mmol) in ethanol (80 mL) was added 1,3-diethyl propanedioate (13 g, 82 mmol) and piperidine (0.87 g, 10 mmol) was added dropwise. The reaction mixture was stirred at 80 °C for 18 hours. After completion of reaction, the reaction mixture was cooled to room temperature and filtered. The solid mass was dried under vacuum to afford ethyl 2-hydroxy-1,6-naphthyridine-3-carboxylate as an off-white solid.

Synthesis of ethyl 2-chloro-1,6-naphthyridine-3-carboxylate



[00414] Mixture of ethyl 2-hydroxy-1,6-naphthyridine-3-carboxylate (2 g, 9.2 mmol) and phosphorous(V) oxychloride (20 mL) was heated at 130 °C for 18 hours under nitrogen atmosphere. After completion of reaction, the crude material was concentrated under reduced pressure. The reaction mixture was quenched with aqueous sodium carbonate and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford ethyl 2-chloro-1,6-naphthyridine-3-carboxylate as a light yellow solid.

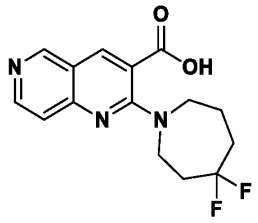
Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylate



[00415] To a solution of ethyl 2-chloro-1,6-naphthyridine-3-carboxylate (0.8 g, 3.4 mmol) in *N,N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrogen chloride (0.9 g, 5.1 mmol) and potassium carbonate (1.9 g, 13.5 mmol). The resulting reaction mixture was heated at 80 °C for 16 hours under nitrogen atmosphere. The progress of reaction was

monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford ethyl 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylate as light yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylic acid



[00416] To a solution of ethyl 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylate (0.75 g, 2.3 mmol) in a mixture of methanol (25 mL) and tetrahydrofuran (25 mL) was added a solution of lithium hydroxide monohydrate (0.4 g, 9.2 mmol) in water (25 mL). The mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with water followed by treatment with 1 N hydrochloric acid solution and extracted with 10% isopropanol in chloroform. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was triturated with diethyl ether and n-pentane to afford 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylic acid as a light yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,6-naphthyridine-3-carboxamide

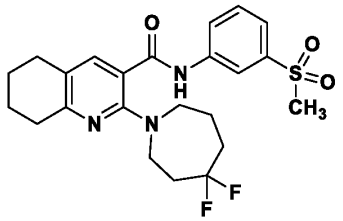
[00417] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylic acid (0.25 g, 0.8 mmol) in dichloromethane (20 mL) was added bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) (0.46 g, 1.2 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP) (0.049 g, 0.41 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 18 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, dichloromethane was removed under reduced pressure. The resulting residue was diluted with acetonitrile (20 mL) and to this mixture, 3-aminobenzenesulfonamide (0.17 g, 1 mmol) was added and stirred at 70

°C for 18 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-10% methanol in dichloromethane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-1,6-naphthyridine-3-carboxamide as a light yellow solid. MS (ESI): Calcd $[M+H]^+$: 462.14, found: 462.30

[00418] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 9.07 (s, 1H), 8.52-8.49 (m, 2H), 8.30 (m, 1H), 7.86-7.84 (m, 1H), 7.59-7.55 (m, 2H), 7.46-7.42 (m, 3H), 7.95 (s, 1H), 3.85-3.75 (m, 2H), 3.65-3.61 (m, 2H), 2.42-2.33 (m, 2H), 2.03-1.91 (m, 2H), 1.89 (s, 2H)

Compound 22

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

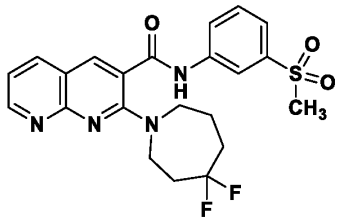


[00419] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.20 g, 0.64 mmol) in dichloromethane (4 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.38 g, 1 mmol) and 4-dimethylaminopyridine (0.004 g, 0.03 mmol) at 0 ℃ and stirred the mixture at room temperature for 12 hours. After completion of reaction, dichloromethane was evaporated under reduced pressure and the crude residue was dissolved into acetonitrile (4 mL) and to this mixture, 3-(methylsulfonyl)aniline (0.19 g, 1.1 mmol) was added and heated to reflux for 12 hours. After completion of reaction, acetonitrile was removed under rotatory evaporation and the crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by preparative HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfonyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 464.18, found: 464.30

[00420] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.34 (s, 1H), 7.96-7.95 (m, 1H), 7.63-7.59 (m, 2H), 7.45 (s, 1H), 3.57-3.56 (m, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.2 (s, 3H), 2.70-2.67 (m, 2H), 2.65-2.62 (m, 2H), 2.35-2.26 (m, 2H), 2.00-1.93 (m, 2H), 1.83-1.79 (m, 4H), 1.77-1.73 (m, 2H).

Compound 23

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-1,8-naphthyridine-3-carboxamide

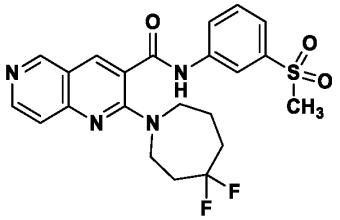


[00421] To a stirred suspension of 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid (0.2 g, 0.65 mmol) in dry dichloromethane (10 mL), [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (0.37 g, 0.98 mmol) and *N,N*-dimethylpyridin-4-amine (0.039 g, 0.325 mmol) were added sequentially at 0 °C. The resulting mixture was stirred at room temperature for 18 hours. Afterwards, reaction mixture was evaporated under vacuum to remove the dichloromethane and the resulting residue was dissolved in acetonitrile (10 mL) and this solution, 3-(methylsulfonyl)aniline (0.13 g, 0.78 mmol) was added and heated at 80 °C for 18 hours. After completion of reaction, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude. The crude product was purified by flash column chromatography with a gradient of 100% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfonyl)phenyl)-1,8-naphthyridine-3-carboxamide as a light yellow solid. MS (ESI): Calcd $[M+H]^+$: 461.15, found: 461.30.

[00422] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H), 8.85-8.83 (m, 1H), 8.43 (s, 1H), 8.36-8.34 (m, 1H), 8.27-8.25 (m, 1H), 8.02-8.00 (m, 1H), 7.70-7.65 (m, 2H), 7.33-7.30 (m, 1H), 3.85-3.75 (m, 2H), 3.64-3.63 (m, 2H), 3.23 (s, 3H), 2.44-2.40 (m, 2H), 2.07-2.00 (m, 2H), 1.96-1.91 (m, 2H)

Compound 24

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-1,6-naphthyridine-3-carboxamide

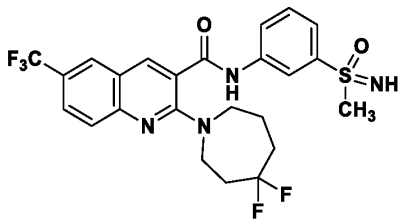


[00423] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylic acid (0.25 g, 0.81 mmol) in dichloromethane (5 mL) was added Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.46 g, 1.2 mmol) and *N,N*-dimethylpyridin-4-amine (0.05 g, 0.41 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 5 hours. After completion of reaction, solvent was removed under reduced pressure and diluted with acetonitrile (5 mL) and to this, 3-methanesulfonylaniline (0.14 g, 0.81 mmol) was added at room temperature and slowly heated to 70 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfonyl)phenyl)-1,6-naphthyridine-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 461.15, found: 461.3

[00424] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1H), 9.00 (s, 1H), 8.43 (s, 1H), 8.36 (d, J = 4 Hz, 2H), 7.74 (m, 1H), 7.75 (d, J = 4 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.95 (s, 1H), 3.80-3.77 (m, 2H), 3.64 (t, J = 8 Hz, 2H), 3.23 (s, 3H), 2.42-2.39 (m, 2H), 2.00-1.97 (m, 2H), 1.93-1.90 (m, 2H).

Compound 25

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-6-(trifluoromethyl)quinoline-3-carboxamide

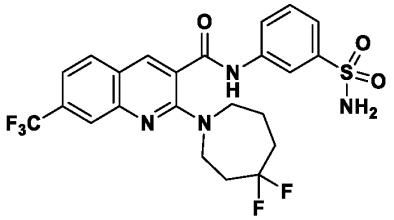


[00425] To a solution of 2-(4,4-difluoroazepan-1-yl)-6-(trifluoromethyl)quinoline-3-carboxylic acid (0.2 g, 0.53 mmol) in dry dichloromethane (6.0 mL) was added oxalyl chloride (0.10 mL, 1.16 mmol) and catalytic amount of *N*,*N*-dimethylformamide (2 drops) under nitrogen atmosphere at 0 °C and the reaction mixture was stirred for 2 hours at room temperature. After completion of reaction, the solvent was removed under nitrogen atmosphere and the crude mixture was dissolved into dry dichloromethane (6 mL) and added to the solution of (3-aminophenyl)(imino)(methyl)-λ^6-sulfanone (0.11 g, 0.64 mmol) and *N*,*N*-diisopropylethyl amine (0.50 mL, 2.65 mmol) in dichloromethane (6 mL) at 0 °C and stirred the mixture for 2 hours at room temperature. The progress of reaction was monitor by TLC. After completion of reaction, the mixture was quenched with water, extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-6-(trifluoromethyl)quinoline-3-carboxamide as a light brown solid. MS (ESI): Calcd $[M+H]^+$: 527.15, found: 527.20.

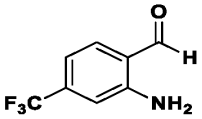
[00426] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.50 (s, 1H), 8.34 (t, J = 2.0 Hz, 1H), 8.30 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 2.0, 8.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 4.23 (s, 1H), 3.97-3.74 (m, 2H), 3.64 (t, J = 5.6 Hz, 2H), 3.07 (s, 3H), 2.45-2.37 (m, 2H), 2.01-1.96 (m, 2H), 1.91-1.90 (m, 2H).

Compound 26

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7-(trifluoromethyl)quinoline-3-carboxamide

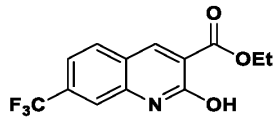


Synthesis of 2-amino-4-(trifluoromethyl)benzaldehyde



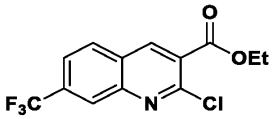
[00427] To a stirred solution of 2-nitro-4-(trifluoromethyl)benzaldehyde (5 g, 23 mmol) in ethanol (50 mL) was added iron powder (13.2 g, 22.8 mmol) and conc. HCl (0.6 mL) at room temperature and slowly refluxed for 2 hours. After completion of reaction, the reaction mixture was filtered through Celite and solvent was removed by rotary evaporation and diluted with water and then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude material was triturated with *n*-pentane to afford 2-amino-4-(trifluoromethyl)benzaldehyde as pale yellow solid.

Synthesis of ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate



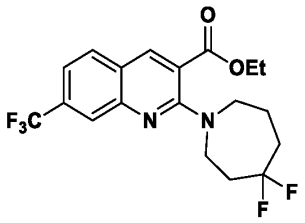
[00428] To a stirred solution of 2-amino-4-(trifluoromethyl)benzaldehyde (2 g, 11 mmol) in ethanol (20 mL) was added diethyl malonate (13.8 g, 105.7 mmol) and piperidine (5.3 mL, 52.9 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 hours. After completion of reaction, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and triturated with diethyl ether to afford ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate as an off-white solid.

Synthesis of ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate



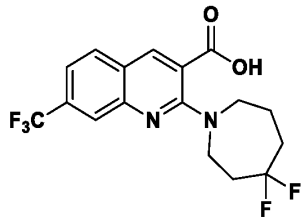
[00429] A mixture of ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate (1 g, 11 mmol) and phosphorous oxychloride (10 mL) was slowly heated to 120 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with ice-water followed by saturated sodium bicarbonate solution, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude material which was triturated with *n*-pentane to afford ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate as a brown oil.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate



[00430] To a solution of ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate (0.5 g, 1.65 mmol) in *N*,*N*-dimethylformamide (5 mL) was added 4,4-difluoroazepane hydrogen chloride (0.42 g, 2.5 mmol) and potassium carbonate (0.9 g, 6.6 mmol) at room temperature. The reaction mixture was heated at 80 °C for 16 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion, the crude material was diluted with water, extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude material which was purified by flash column chromatography with a gradient of 50-70% EtOAc in hexanes to afford ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid



[00431] To a stirred solution of ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate (0.5 g, 1.2 mmol) in a mixture of methanol (8 mL) and THF (8 mL) was added a solution of lithium hydroxide (0.12 g, 5 mmol) in water (8 mL) at 0 ℃ and stirred at room temperature for 24 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of reaction, solvent was removed by rotary and diluted with ice-water followed by treatment with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and resultant crude was triturated with *n*-pentane and diethyl ether to afford 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid as a brownish white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7-(trifluoromethyl)quinoline-3-carboxamide

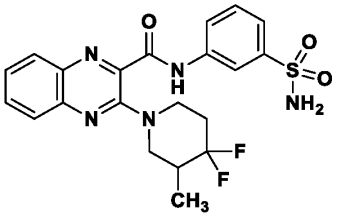
[00432] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid (0.28 g, 0.75 mmol) in dichloromethane (8 mL), (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.43 g, 1.1 mmol) and 4-dimethylamino pyridine (DMAP) (0.048 g, 0.37 mmol) was added at 0 ℃ and stirred at room temperature for 12 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of reaction, solvent was removed in vacuo and diluted with acetonitrile (3 mL) and added to the solution of 3-aminobenzenesulfonamide (0.16 g, 0.9 mmol) in acetonitrile (8 mL). The reaction mixture was heated at 80 °C for 12 hours. Then progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-

sulfamoylphenyl)-7-(trifluoromethyl)quinoline-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 529.13, found: 529.25.

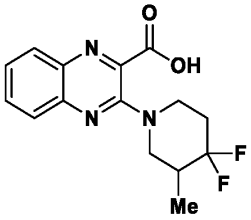
[00433] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 8.48 (s, 1H), 8.31(s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.85-7.87 (m, 1H), 7.54-7.60- (m, 3H), 7.43 (brs, 2H), 3.80-3.79 (m, 2H), 3.64 (t, J = 6 Hz, 2H), 2.33-2.43 (m, 2H), 1.91-2.0 (m, 4H).

Compound 27

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide



Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxylic acid



[00434] To a mixture of 3-chloroquinoxaline-2-carboxylic acid (180 mg, 0.87 mmol) and 4,4-difluoro-3-methylpiperidine hydrogen chloride (160 mg, 0.87 mmol) in *N,N*-dimethylformamide (4 mL), potassium carbonate (600 mg, 4.3 mmol) was added at room temperature. The reaction mixture was stirred at 70 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic layers were combined and washed with brine. The organic layer then was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography with a gradient of 0-50% methanol in dichloromethane to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxylic acid as a yellow oil.

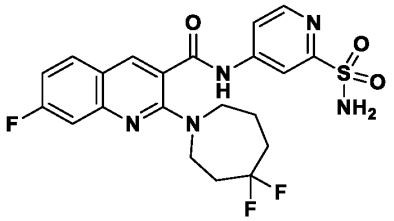
Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide

[00435] To a stirred solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxylic acid (44 mg, 0.14 mmol) in dichloromethane (2 mL), (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (81 mg, 1.4 mmol) and 4-dimethylamino pyridine (DMAP) (52 mg, 0.43 mmol) was added at room temperature and stirred at room temperature for 18 hours. The progress of reaction mixture was monitored by TLC and LCMS. Then progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure and the crude residue was purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(3-sulfamoylphenyl)quinoxaline-2-carboxamide as a white solid. LRMS (ESI): Calcd $[M+H]^+$: 462.14, found: 461.9.

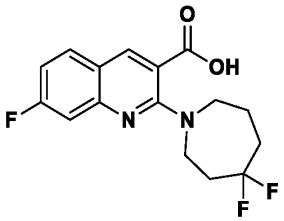
[00436] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.32 (t, *J* = 2.0 Hz, 1H), 8.11 – 8.06 (m, 1H), 7.99 – 7.94 (m, 1H), 7.83 – 7.79 (m, 1H), 7.76 – 7.71 (m, 2H), 7.60 – 7.54 (m, 2H), 4.90 (s, 2H), 4.09 – 3.95 (m, 2H), 3.40 – 3.31 (m, 1H), 3.16 – 3.07 (m, 1H), 2.33 – 2.19 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H).

Compound 28

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

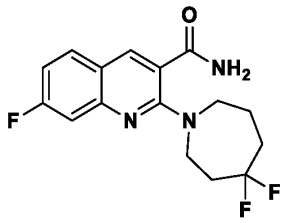


Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid



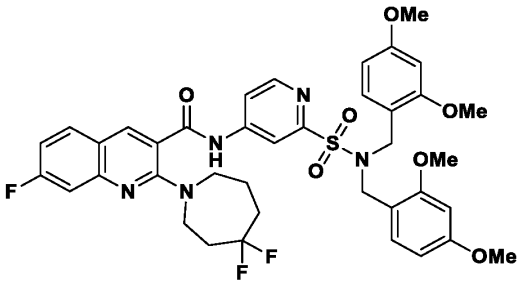
[00437] To a mixture of 2-chloro-7-fluoroquinoline-3-carboxylic acid (115 mg, 0.51 mmol) and 4,4-difluoroazepane hydrogen chloride (88 mg, 0.51 mmol) in *N,N*-dimethylformamide (4 mL), potassium carbonate (352 mg, 2.55 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C for 18 hours. After completion, the reaction mixture was diluted with hydrochloric acid 1 N and extracted with dichloromethane. The organic layer then was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography with a gradient 0 to 20% methanol in dichloromethane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid as a yellow oil.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



[00438] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (81 mg, 0.25 mmol) in dichloromethane (2 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.14 g, 0.37 mmol) and ammonium carbonate (120 mg, 1.25 mmol) at room temperature. The reaction mixture was stirred at room temperature for 72 hours. After completion of reaction, the reaction mixture was diluted with water and extracted dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography using a Combiflash with a gradient of 0 to 100% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a yellow powder.

Synthesis of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



[00439] 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (13.5 mg, 0.042 mmol), 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (22.4 mg, 0.042 mmol), cesium carbonate (27 mg, 0.084 mmol), and BrettPhos Pd G3 (4 mg, 0.0042 mmol) were added to a flame dried round bottom flask and capped. The reaction vessel was evacuated and the atmosphere was replace with nitrogen. Then, degassed anhydrous dioxane (2 mL) was added to the reaction vessel and the mixture was stirred at 100 ºC for 18 hours. Dioxane was removed in vacuo and the crude mixture was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a light yellow oil.

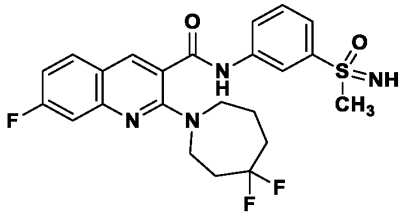
Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00440] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (9 mg, 0.0115 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (500 μL). The reaction mixture was stirred for 18 hours then the volatiles were removed in vacuo. The resulting crude mixture was diluted with water and acetonitrile then purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 480.13, found: 479.8.

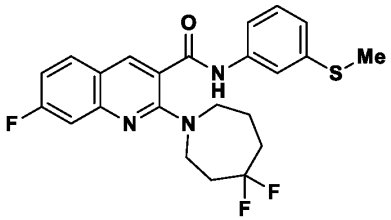
[00441] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.31 (m, 1H), 8.03 – 7.96 (m, 1H), 7.85 – 7.78 (m, 1H), 7.55 – 7.43 (m, 1H), 7.25 – 7.23 (m, 1H), 7.15 – 7.06 (m, 1H), 6.92 – 6.80 (m, 1H), 3.67 – 3.51 (m, 2H), 3.44 – 3.26 (m, 2H), 2.34 – 2.12 (m, 2H), 1.95 – 1.61 (m, 4H).

Compound 29

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-(methylthio)phenyl)quinoline-3-carboxamide



[00442] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (41.4 mg, 0.13 mmol) in dichloromethane (2 mL) and N,N-dimethylformamide (2 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (73 mg, 0.19 mmol) and 4-dimethylaminopyridine (DMAP) (47 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 15 minutes. Then, 3-(methylthio)aniline (15.7 µL, 0.13 mmol) was added to the reaction mixture and stirred at room temperature for 18 hours. Then the reaction mixture was stirred at 60 °C for 72 hours. After the completion of reaction, dichloromethane was removed in vacuo and the resulting mixture was purified by flash column chromatography with a gradient of 0 to 50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(3-(methylthio)phenyl)quinoline-3-carboxamide as a yellow oil.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide

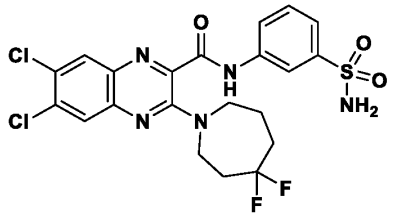
[00443] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(3-(methylthio)phenyl)quinoline-3-carboxamide (57 mg, 0.13 mmol) in MeOH (10 mL) was added ammonium carbonate (43 mg, 0.45 mmol) then (diacetoxyiodo)benzene (125 mg, 0.384 mmol). The reaction mixture was stirred at 60 °C for 18 hours. The progress of the reaction

was monitored by LCMS. Methanol was removed in vacuo and the resulting crude mass was diluted with water and acetonitrile and purified using reversed-phase HPLC with a gradient of 0-50% acetonitrile in water to afford 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)quinoline-3-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 477.16, found: 476.9.

[00444] ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.06 (m, 2H), 8.02 – 7.94 (m, 1H), 7.69 – 7.56 (m, 2H), 7.54 – 7.45 (m, 1H), 7.24 – 7.23 (m, 1H), 7.02 – 6.94 (m, 1H), 3.70 – 3.67 (m, 2H), 3.58 – 3.48 (m, 2H), 3.12 – 3.00 (s, 3H), 2.44 – 2.26 (m, 2H), 2.04 – 1.81 (m, 4H).

Compound 30

Synthesis of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoxaline -3-carboxamide

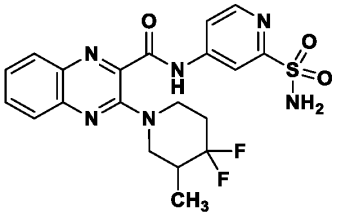


[00445] To a stirred solution of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoxaline-3-carboxylic acid (15 mg, 0.04 mmol) in dichloromethane (2 mL) and N,N-dimethylformamide (0.5 mL), (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (HATU) (23 mg, 0.12 mmol), 4-dimethylamino pyridine (DMAP) (15 mg, 0.12 mmol) was added at room temperature and stirred at room temperature for 15 minutes. Then 3-aminobenzenesulfonamide (7 mg, 0.04 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 18 hours then at 60 °C for 18 hours. Dichloromethane was removed in vacuo and the crude residue was purified by reversed-phase HPLC with a gradient of 30-80% acetonitrile in water to afford 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide an off-white solid. LRMS (ESI): Calcd $[M+H]^+$: 530.06, found: 529.7.

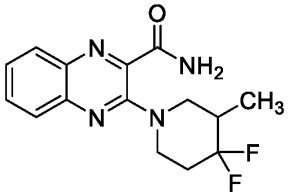
[00446] ^1H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.89-7.86 (m, 1H), 7.63-7.58 (m, 2H), 7.41 (br s, 2H), 3.82-3.79 (m, 2H), 3.67 (t, J = 6.0 Hz, 2H), 2.41-2.36 (m, 2H), 2.07-1.99 (m, 2H), 1.93-1.75 (m, 2H).

Compound 31

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide

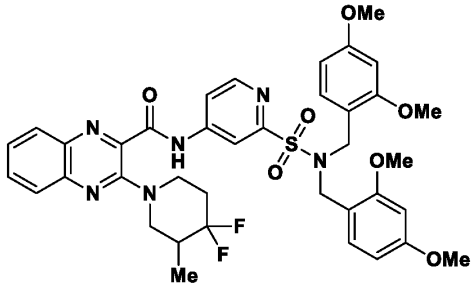


Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamide



[00447] To a stirred solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxylic acid (215 mg, 0.7 mmol) in dichloromethane (5 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.4 g, 1.05 mmol) and ammonium carbonate (330 mg, 3.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was diluted with water and extracted dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography using a Combiflash with a gradient of 0 to 50% ethyl acetate in hexanes to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamide as a light yellow powder.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamide



[00448] 3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamide (31 mg, 0.1 mmol), 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (54 mg, 0.1 mmol), cesium carbonate (65 mg, 0.2 mmol), and BrettPhos Pd G3 (18 mg, 0.01 mmol) were added to a flame dried round bottom flask and capped. The reaction vessel was evacuated and the atmosphere was replace with nitrogen. Then, degassed anhydrous dioxane (2 mL) was added to the reaction vessel and the mixture was stirred at 100 °C for 18 hours. Dioxane was removed in vacuo and the crude mixture was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamideas a yellow foam.

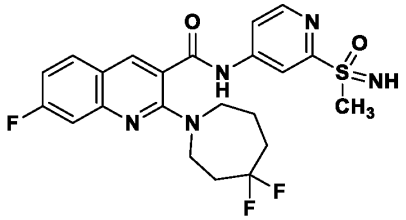
Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2- carboxamide

[00449] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)quinoxaline-2-carboxamide (70 mg, 0.091 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (140 µL). The reaction mixture was stirred for 18 hours then the volatiles were removed in vacuo. The resulting crude mixture was diluted with water and acetonitrile then purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 463.14, found: 462.9.

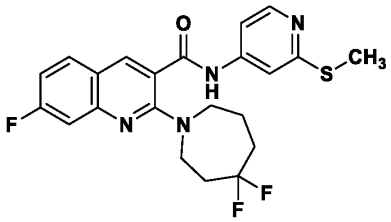
[00450] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.45 (m, 1H), 8.22 – 8.07 (m, 2H), 7.94 – 7.84 (m, 1H), 7.78 – 7.60 (m, 2H), 7.56 – 7.41 (m, 1H), 4.20 – 3.49 (m, 3H), 3.01 (s, 2H), 2.13 (s, 2H), 0.99 (s, 3H).

Compound 32

Synthesis of 2-(4,4-difluoro-azepan-1-yl)-7-fluoro-N-(2-(S-methylsulfonimidoyl)pyridin-4-yl)quinoline-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(methylthio)pyridin-4-yl)quinoline-3-carboxamide



[00451] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (41 mg, 0.13 mmol), 4-chloro-2-(methylthio)pyridine (20.5 mg, 0.13 mmol), cesium carbonate (83.6 mg, 0.26 mmol), and BrettPhos Pd G3 (23 mg, 0.026 mmol) were added to a flame dried round bottom flask and capped. The reaction vessel was evacuated and the atmosphere was replace with nitrogen. Then, degassed anhydrous dioxane (2 mL) was added to the reaction vessel and the mixture was stirred at 100 °C for 18 hours. Dioxane was removed in vacuo and the crude mixture was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(methylthio)pyridin-4-yl)quinoline-3-carboxamide as a yellow oil.

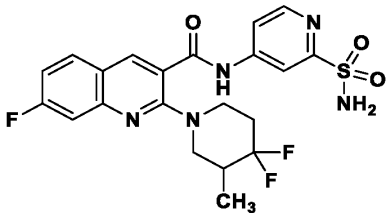
Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(S-methylsulfonimidoyl)pyridin-4-yl)quinoline-3-carboxamide

[00452] To a stirred solution of 2-(4,4-difluoro*azepan*-1-yl)-7-fluoro-N-(2-(methylthio)pyridin-4-yl)quinoline-3-carboxamide (57 mg, 0.13 mmol) in MeOH (10 mL) was added ammonium carbonate (43 mg, 0.45 mmol) then (diacetoxyiodo)benzene (120 mg, 0.38 mmol). The reaction mixture was stirred at 50 °C for 24 hours. The progress of the reaction was monitored by LCMS. Methanol was removed in vacuo and the resulting crude mass was

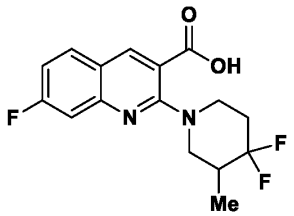
diluted with water and acetonitrile and purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(S-methylsulfonimidoyl)pyridin-4-yl)quinoline-3-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 478.15, found 477.9.

Compound 33

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

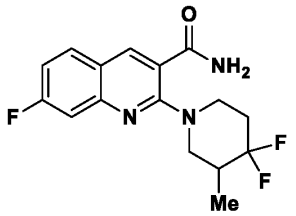


Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid



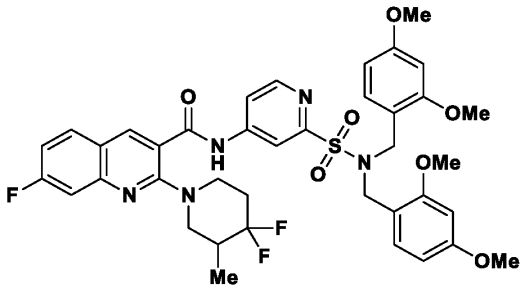
[00453] To a mixture of 2-chloro-7-fluoroquinoline-3-carboxylic acid (113 mg, 0.5 mmol) and 4,4-difluoro-3-methylpiperidine hydrogen chloride (86 mg, 0.5 mmol) in *N,N*-dimethylformamide (2 mL), potassium carbonate (345 mg, 2.5 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C for 72 hours. After completion, the reaction mixture was diluted with hydrochloric acid 1 N and extracted with dichloromethane. The organic layer then was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography with a gradient methanol in dichloromethane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid as an orange solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide



[00454] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (65 mg, 0.2 mmol) in dichloromethane (2 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.114 g, 0.3 mmol) and ammonium carbonate (96 mg, 1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was diluted with water and extracted dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography using a Combiflash with a gradient of ethyl acetate in hexanes to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide as a light yellow oil.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide



[00455] 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (20.6 mg, 0.064 mmol), 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (34 mg, 0.064 mmol), cesium carbonate (41.5 mg, 0.127 mmol), and BrettPhos Pd G3 (12 mg, 0.013 mmol) were added to a flame dried round bottom flask and capped. The reaction vessel was evacuated and the atmosphere was replace with nitrogen. Then, degassed anhydrous dioxane (2 mL) was added to the reaction vessel and the mixture was stirred at 100 ºC for 18 hours.

Dioxane was removed in vacuo and the crude mixture was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide as a yellow oil.

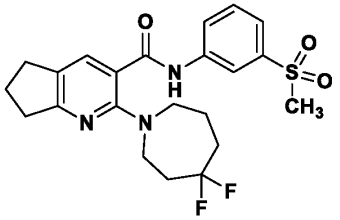
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00456] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (40 mg, 0.052 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (80 µL). The reaction mixture was stirred for 18 hours then the volatiles were removed in vacuo. The resulting crude mixture was diluted with water and acetonitrile then purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 480.13, found: 479.8.

[00457] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (t, *J* = 4.7 Hz, 1H), 8.19 (d, *J* = 4.2 Hz, 1H), 8.10 – 7.97 (m, 1H), 7.86 – 7.73 (m, 1H), 7.65 – 7.49 (m, 1H), 7.03 – 6.90 (m, 1H), 3.74 – 3.53 (m, 2H), 2.89 – 2.77 (m, 1H), 2.13 – 1.71 (m, 4H), 0.87 – 0.70 (m, 3H).

Compound 34

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl) phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide



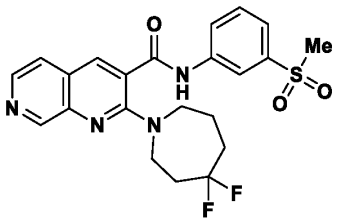
[00458] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid (0.15 g, 0.5 mmol) in dichloromethane (6 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) (0.38 g, 1 mmol) and 4-(dimethylamino)pyridine (0.03 g, 0.25 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with acetonitrile (6

mL) and to this, 3-(methyl sulfonyl) aniline (0.1 g, 0.6 mmol) was added and heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, acetonitrile was removed under rotatory evaporation. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfonyl)phenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 450.17, found: 450.25

[00459] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.35 (s, 1H), 7.95 (d, J = 6.0 Hz, 1H), 7.62-7.59 (m, 3H), 3.58 (s, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.20 (s, 3H), 2.83-2.79 (m, 4H), 2.36-2.27 (m, 2H), 2.08-2.03 (m, 2H), 2.01-1.91 (m, 2H), 1.83-1.81 (m, 2H).

Compound 35

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-1,7-naphthyridine-3-carboxamide



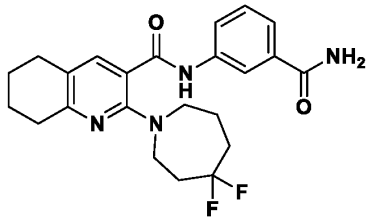
[00460] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid (0.25 g, 0.8 mmol) in dry dichloromethane (5 mL) was added Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.46 g, 1.2 mmol) and *N*,*N*-dimethylpyridin-4-amine (0.05 g, 0.4 mmol) at 0 °C and reaction mixture was stirred at room temperature for 12 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of reaction, solvent was evaporated under rotatory evaporation and diluted with acetonitrile (5 mL) and to this, 3-methanesulfonylaniline (0.17 g, 0.97 mmol) was added at room temperature. The reaction mixture was stirred at 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes

to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfonyl)phenyl)-1,7-naphthyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 461.15, found: 461.30

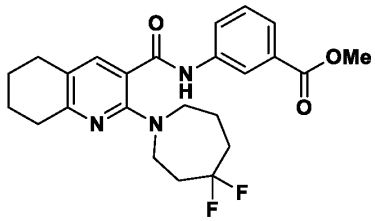
[00461] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1H), 9.00 (s, 1H), 8.43 (s, 1H), 8.36 (d, J = 4 Hz, 2H), 8.02-7.99 (m, 1H), 7.75 (d, J = 4 Hz, 1H), 7.72-7.66 (m, 2H), 3.80-3.77 (m, 2H), 3.64 (t, J = 4 Hz, 2H), 3.23 (s, 3H), 2.42-2.39 (m, 2H), 2.06-1.97 (m, 2H), 1.93-1.90 (m, 2H).

Compound 36

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamido) benzoate



[00462] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.25 g, 0.8 mmol) in dichloromethane (10 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.45 g, 1.2 mmol) and 4-dimethylaminopyridine (DMAP) (0.005 g, 0.04 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, dichloromethane was evaporated under reduced pressure. The resulting mass was dissolved into acetonitrile (5 mL) and to this methyl 3-aminobenzoate (0.14 g, 0.96 mmol) was added at room temperature and heated at 80 °C for 12 hours. After completion of reaction, acetonitrile was removed in vacuo. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated under rotatory. The crude material was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford

methyl 3-(2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamido) benzoate as a white solid.

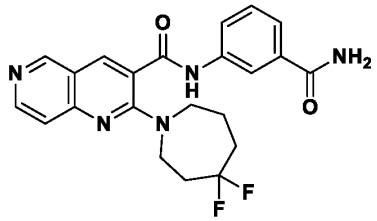
Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00463] A solution of methyl 3-(2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamido) benzoate (0.15 g, 0.3 mmol) in 7 N ammonia in methanol (5 mL) was heated at 100 °C for 48 hours. The progress of reaction was monitored by TLC. After completion of reaction, methanol was removed under reduced pressure. The crude material was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexanes to afford *N*-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid. MS (ESI): Calcd $[M+H]^+$: 429.21, found: 429.35.

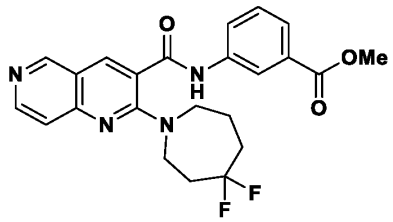
[00464] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.15 (s, 1H), 7.93 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.41-7.35 (m, 3H), 3.57-3.56 (m, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.69-2.66 (m, 2H), 2.65-2.62 (m, 2H), 2.31-2.24 (m, 2H), 1.98-1.190 (m, 2H), 1.81-1.79 (m, 4H), 1.73-1.72 (m, 2H).

Compound 37

Synthesis N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamide



Synthesis methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate



[00465] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid (0.50 g, 1.6 mmol) in dry dichloromethane (20 mL) was added

Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (0.93 g, 2.4 mmol) and *N,N*-dimethylpyridin-4-amine (0.1 g, 0.82 mmol) was added at 0 ℃. The reaction mixture was stirred at room temperature for 16 hours. The reaction progress of reaction was monitored by TLC and LCMS. After completion of reaction, solvent was evaporated under rotatory evaporation and diluted with acetonitrile (10 mL) and to this solution, methyl 3-aminobenzoate (0.25 g, 2 mmol) and stirred the reaction mixture at 70 ℃ for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in heptane to afford methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate as a white solid.

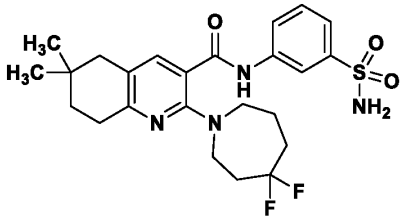
Synthesis N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamide

[00466] Methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate (0.50 g, 1.1 mmol) was dissolved into 7*N* Ammonia in methanol (10 mL) and heated to 80 ℃ for 12 hours. The progress of reaction was monitored by TLC and LCMS. After completion of the reaction, mixture was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 0-5% methanol in dichloromethane to afford *N*-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 426.17, found: 426.30

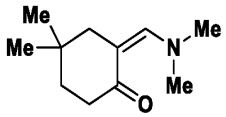
[00467] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 9.07 (s, 1H), 8.51 (d, J = 4 Hz, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 7.97 (s, 1H), 7.87 (d, J = 8 Hz ,1H), 7.63 (d, J = 8 Hz, 1H), 7.468 (s, 1H), 7.46 (t, J= 8 Hz, 1H), 7.38 (s, 1H), 3.82-3.80 (m, 2H), 3.67 (t, J = 8 Hz, 2H), 2.42-2.39 (m, 2H), 2.02-1.99 (m, 2H), 1.92-1.90 (m, 2H).

Compound 38

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

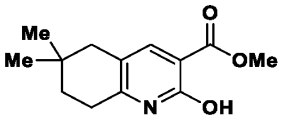


Synthesis of (Z)-2-((dimethylamino)methylene)-4,4-dimethylcyclohexan-1-one



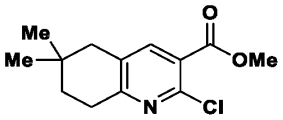
[00468] To a stirred solution of 4,4-dimethylcyclohexan-1-one (10 g, 79 mmol) in toluene (50 mL), [(tert-butoxy)(dimethylamino)methyl]dimethylamine (15 g, 87 mmol) was added and the resulting mixture was stirred at 50 °C for 24 hours. Progress of the reaction was monitored by LCMS. After completion of the reaction, the reaction mixture was evaporated under vacuum to afford the crude *(Z)*-2-((dimethylamino)methylene)-4,4-dimethylcyclohexan-1-one as a brown liquid. The crude product was used as such in the next step without purification.

Synthesis of methyl 2-hydroxy-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



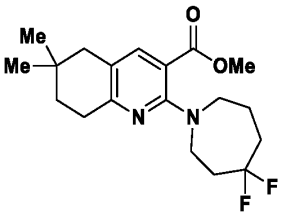
[00469] To a stirred solution of crude *(Z)*-2-((dimethylamino)methylene)-4,4-dimethylcyclohexan-1-one (15 g, 83 mmol) in methanol (75 mL), methyl 2-cyanoacetate (9.8 g, 99 mmol) was added and the resulting mixture was heated at 70 °C for 24 hours. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, methanol was removed under reduced pressure and the resulting residue was purified by trituration with acetonitrile to afford methyl 2-hydroxy-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



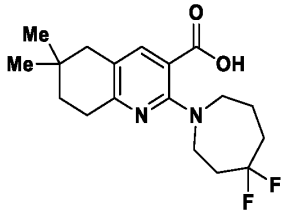
[00470] A solution of methyl 2-hydroxy-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (6 g, 26 mmol) in phosphoryl oxychloride (60 mL) was heated at 130 °C for 18 hours under nitrogen atmosphere. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under reduced pressure and then poured into a beaker containing crushed ice. The mixture was basified with aqueous sodium bicarbonate and then extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude product. The crude material was purified by flash column chromatography with a gradient of 10- 15% ethyl acetate in hexanes to afford methyl 2-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a yellow oil.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00471] To a stirred solution of methyl 2-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (2.0 g, 7.9 mmol) in *N,N*-dimethylformamide (10 mL), 4,4-difluoroazepane hydrochloride (2.7 g, 15.8 mmol) and dipotassium carbonate (6.5 g, 47.4 mmol) were added at room temperature. The resulting mixture was heated at 100 °C for 24 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 5-10% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a yellow viscous oil.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00472] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (1 g, 2.8 mmol) in methanol (20 mL) and tetrahydrofuran (20 mL), aqueous solution of lithium hydroxide (0.48 g, 11.4 mmol) in water (20 mL) was added. The resulting mixture was stirred at room temperature for 24 hours. Progress of the reaction was monitored by TLC. The organic solvents were removed under the reduced pressure and the resulting aqueous solution was acidified with 1*N* hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product. The crude product was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in heptane to afford 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

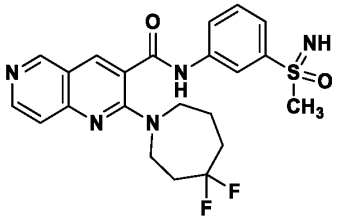
[00473] To a stirred suspension of 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.3 g, 0.9 mmol) in dichloromethane (10 mL) was added [Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (0.5 g, 1.3 mmol) and *N,N*-dimethylpyridin-4-amine (0.054 g, 0.44 mmol) were added sequentially between 0-5 °C. The resulting mixture was stirred at room temperature for 16 hours. The progress of reaction was monitored by TLC. After completion of the reaction, mixture was evaporated under vacuum to remove the dichloromethane and the resulting residue was dissolved into acetonitrile (10 mL). To this solution, 3-aminobenzene-1-sulfonamide (0.18 g, 1 mmol) was added and reaction mixture was heated at 80 °C for 16 hours. After the completion of reaction, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried

over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in heptane to afford 2-(4,4-difluoroazepan-1-yl)-6,6-dimethyl-*N*-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 493.21, found: 493.00

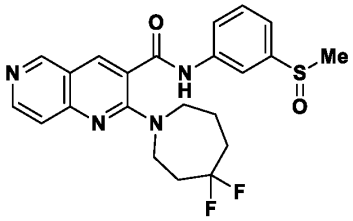
[00474] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.30 (s, 1H), 7.80-7.77 (m, 1H), 7.54-7.49 (m, 2H), 7.39-7.37 (m, 3H), 3.58-3.56 (m, 2H), 3.41-3.38 (m, 2H), 2.72-2.68 (m, 2H), 2.43 (s, 2H), 2.29-2.26 (m, 2H), 1.97-1.90 (m, 2H), 1.81-1.80 (m, 2H), 1.61-1.58 (m, 2H), 0.96 (s, 6H).

Compound 39

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,6-naphthyridine-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-1,6-naphthyridine-3-carboxamide



[00475] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxylic acid (0.10 g, 0.325 mmol) in dry dichloromethane (5 mL) was added Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.19 g, 0.5 mmol) and *N,N*-dimethylpyridin-4-amine (0.02 g, 0.16 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was monitored by TLC and LCMS. After completion of reaction, solvent was removed in vacuo and diluted with acetonitrile (5 mL) and to this solution, 3-methanesulfinylaniline (0.06 g, 0.39 mmol) was added at room temperature and the reaction

mixture was heated at 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-1,6-naphthyridine-3-carboxamide as a white solid.

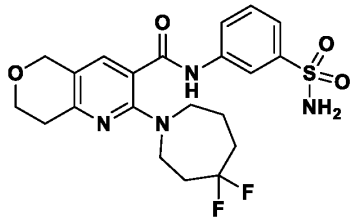
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,6-naphthyridine-3-carboxamide

[00476] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-1,6-naphthyridine-3-carboxamide (0.100 g, 0.225 mmol) in Eaton's Reagent (1 mL) was added sodium azide (0.03 g, 0.45 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 2 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of the reaction, the mixture was diluted with water and basified by using sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 0-5% methanol in dichloromethane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-1,6-naphthyridine-3-carboxamide a white solid. MS (ESI): Calcd $[M+H]^+$: 461.15, found: 460.30

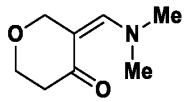
[00477] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 9.07 (s, 1H), 8.52 (d, J = 4 Hz, 1H), 8.49 (s, 1H), 8.337-8.333 (m, 1H), 7.99 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.46 (d, J = 4 Hz, 1H), 4.22 (s, 1H), 3.82-3.79 (m, 2H), 3.65 (t, J = 4 Hz, 2H), 3.07 (s, 3H), 2.42-2.39 (m, 2H), 2.01-2.00 (m, 2H), 1.96-1.90 (m, 2H).

Compound 40

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxamide

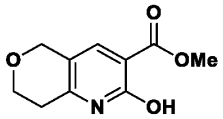


Synthesis of (Z)-3-((dimethylamino)methylene)tetrahydro-4H-pyran-4-one



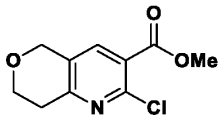
[00478] A mixture of tetrahydro-4*H*-pyran-4-one (5 g, 5 mmol) and 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (9.6 g, 55 mmol) was stirred at room temperature for overnight. Afterwards, heated the reaction mixture at 70 °C for 24 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed under rotatory to obtain crude (*Z*)-3-((dimethylamino)methylene)tetrahydro-4*H*-pyran-4-one as a brown liquid which was used as such into next step without any purification.

Synthesis of methyl 2-hydroxy-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylate



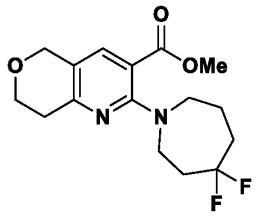
[00479] To the crude (*Z*)-3-((dimethylamino)methylene)tetrahydro-4*H*-pyran-4-one (7 g, 45 mmol) in methanol (35 mL) was added methyl 2-cyanoacetate (4.8 mL, 54 mmol) and reflux the reaction mixture for 24 hours. After completion of reaction, the solvent was removed under rotatory and the resultant crude residue was purified by trituration with acetonitrile to afford methyl 2-hydroxy-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate as a light yellow solid.

Synthesis of methyl 2-chloro-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylate



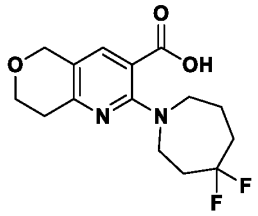
[00480] Methyl 2-hydroxy-7,8-dihydro-5*H*-pyrano[4,3-b]pyridine-3-carboxylate (6 g, 29 mmol) was dissolved into phosphorus oxychloride (60 mL) at room temperature and the reaction mixture was heated at 130 °C for 18 hours. After completion of reaction, the reaction mixture was then cooled to room temperature and excess of phosphorus oxychloride was distilled in vacuo. The residue thus obtained was dissolved into ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate and concentrated in vacuum to afford the crude material which was triturated with diethyl ether and n-pentane to afford methyl 2-chloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate as a white solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylate



[00481] To a solution of methyl 2-chloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (3 g, 13 mmol) in *N*,*N*-dimethylformamide (25 mL) was added 4,4-difluoroazepane hydrogen chloride (4.5 g, 26 mmol) and potassium carbonate (11 g, 79 mmol). The reaction mixture was heated at 130 °C for 28 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylic acid



[00482] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (2.2 g, 6.7 mmol) in tetrahydrofuran (22 mL) and methanol (22 mL) was added aqueous solution of lithium hydroxide (0.57 g, 13.6 mmol) in water (22 mL) and stirred at room temperature for 12 hours. After completion of reaction, solvent was removed under rotatory and diluted with water, acidified with 1*N* hydrochloric solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified

by trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylic acid as an off-white solid.

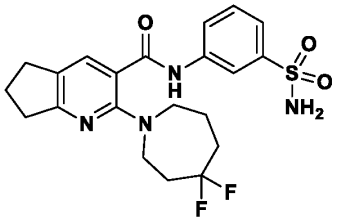
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxamide

[00483] To a solution of 2-(4,4-difluoroazepan-1-yl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylic acid (0.40 g, 1.3 mmol) in dichloromethane (12 mL) was added (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium3-oxid hexafluorophosphate (HATU) (0.730 g, 1.92 mmol) and 4-(dimethylamino) pyridine (0.078 g, 0.64 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with acetonitrile (12 mL) and to this, 3-aminobenzenesulfonamide (0.27 g, 1.5 mmol) was added and heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, acetonitrile was removed under rotatory. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 467.16, found: 467.25

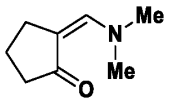
[00484] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 8.29 (brs, 1H), 7.81-7.78 (m, 1H), 7.53-7.50 (m, 2H), 7.46 (s, 1H), 7.39 (brs, 2H), 4.61 (s, 2H), 3.95 (t, J = 5.6 Hz, 2H), 3.61-3.58 (m, 2H), 3.40 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 5.6 Hz, 2H), 2.30-2.27 (m, 2H), 1.97-1.82 (m, 4H).

Compound 41

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide

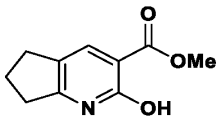


Synthesis of (Z)-2-((dimethylamino)methylene) cyclopentan-1-one



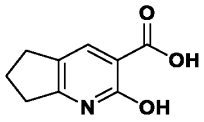
[00485] Cyclopentanone (100 g) was dissolved into 1,1-dimethoxy-*N,N*-dimethylmethanamine (180 mL) and slowly heated to 110 °C for 24 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed under rotatory to obtain the crude (*Z*)-2-((dimethylamino)methylene)cyclopentan-1-one as a brown liquid which was used as such into next step without any purification.

Synthesis of methyl 2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate



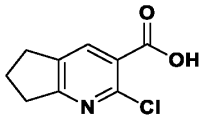
[00486] To the crude (Z)-2-((dimethylamino)methylene) cyclopentan-1-one (150 g) in methanol (75 mL) was added methyl 2-cyanoacetate (114 mL) and heated the reaction mixture at 80 °C for 12 hours. After completion of reaction, the solvent was removed in vacuo and the resultant crude residue was purified by trituration with acetonitrile to afford methyl 2-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylate as light yellow solid.

Synthesis of 2-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid



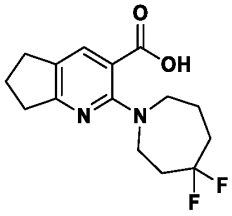
[00487] To a solution of methyl 2-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylate (20 g, 104 mmol) in tetrahydrofuran (20 mL), methanol (20 mL) and water (20 mL) was added lithium hydroxide (8.7 g, 207 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, solvent was removed in vacuo and diluted with water, acidified with 1N hydrochloric solution and extracted with 10% methanol in dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by trituration with diethyl ether and *n*-pentane to afford 2-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid as an off-white solid.

Synthesis of 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid



[00488] To a stirred solution of 2-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid (5 g, 28 mmol) was dissolved into phosphorus oxychloride (50 mL) and heated to 110 °C for 19 hours. Progress of reaction was monitored by TLC. After completion of reaction, mixture was distilled using downward distillation to remove excess phosphorus oxychloride, poured into ice-cold water and extracted with ethyl acetate (2 times). The combined organic layer was washed with cold saturated solution of sodium bicarbonate, brine solution, dried over sodium sulfate, filtered and concentrated to afford the crude material. The crude material was purified through trituration with diethyl ether and n-pentane to afford 2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid as an off-white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid



[00489] To a stirred solution of 2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid (2.5 g, 13 mmol) in *N*,*N*-dimethylformamide (25 mL) was added 4,4-difluoroazepane hydrogen chloride (4.8 g, 28.0 mmol) and dipotassium carbonate (8.8 g, 63.5 mmol). The reaction mixture was heated at 130 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid as a white solid.

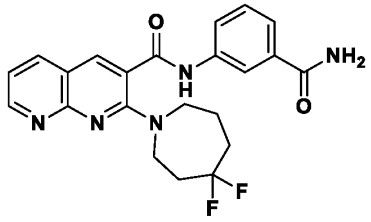
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide

[00490] To a solution of 2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid (0.25 g, 0.84 mmol) in dichloromethane (5 mL) was added (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) (0.064 g, 1.69 mmol) and 4-(dimethylamino) pyridine (0.052 g, 0.42 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with acetonitrile (5 mL) and to this, 3-aminobenzenesulfonamide (0.17 g, 1.2 mmol) was added and heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, acetonitrile was removed in vacuo. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 451.16, found: 451.25

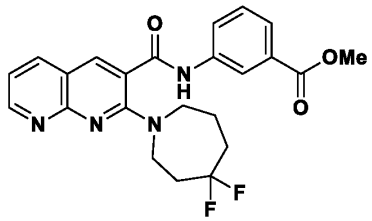
[00491] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.31 (s, 1H), 7.80-7.77 (m, 1H), 7.57 (s, 1H), 7.52-7.51 (m, 2H), 7.39 (s, 2H), 3.58-3.57 (m, 2H), 3.38 (t, J = 6.0 Hz, 2H), 2.81 (m, J = 8.0 Hz, 4H), 2.30-2.26 (m, 1H), 2.08-2.04 (m, 1H), 2.02-1.90 (m, 2H), (m, 2H), 1.82-81 (m, 2H)

Compound 42

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamide

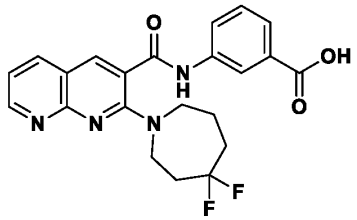


Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoate



[00492] To a solution of 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid (0.15 g, 0.5 mmol) in dichloromethane (5 mL) was added [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (0.28 g, 0.73mmol) and 4-Dimethylaminopyridine (0.003 g, 0.02 mmol) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. After completion of reaction, dichloromethane was evaporated under reduced pressure and resultant crude mass was dissolved into acetonitrile (5 mL) and to this, methyl-3-aminobenzoate (0.082 g, 0.54 mmol) was added and reflux for 12 hours. After completion of reaction, acetonitrile was removed in vacuo. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford methyl-3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoate as a yellow solid.

Synthesis of 3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoic acid



[00493] To a solution of methyl-3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoate (0.15 g, 0.34 mmol) in a mixture of tetrahydrofuran (5 mL) and methanol (5 mL) was added lithium hydroxide (0.029 g, 0.68 mmol) and water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum. The crude mass was dissolved into water (10 mL), acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The combined

organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified through trituration with diethyl ether and n-pentane to obtain 3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoic acid as a yellow solid.

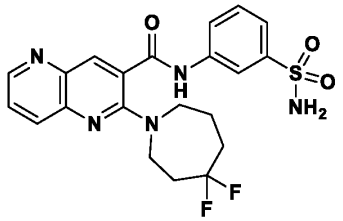
Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamide

[00494] To a solution of 3-(2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamido)benzoic acid (0.10 g, 0.23 mmol) in *N*,*N*-dimethylformamide (5 mL) was added 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-Oxide Hexafluorophosphate (HATU) (0.13 g, 0.35 mmol), *N*,*N*-diisopropylethylamine (0.2 mL, 1.15 mmol) and ammonium chloride (0.12 g, 2.3 mmol) respectively at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified through reversed phase prep-HPLC to afford *N*-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 426.17, found: 426.25

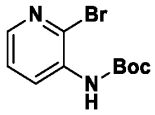
[00495] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 1H), 8.83 (dd, J = 1.6, 4.0 Hz, 1H), 8.37 (s, 1H), 8.26 (dd, J = 1.6, 7.6 Hz, 1H), 8.19 (s, 1H), 7.96 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6, 1H), 7.44 (t, J = 8.4, 1H), 7.38 (s, 1H), 7.32-7.29 (m, 1H), 3.82-3.79 (m, 2H), 3.65 (t, J = 5.6 Hz, 2H), 2.42-2.38 (m, 2H), 2.05-2.00 (m, 2H), 1.96-1.90 (m, 2H).

Compound 43

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-1,5-naphthyridine-3-carboxamide

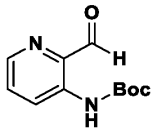


Synthesis of tert-butyl (2-bromopyridin-3-yl)carbamate



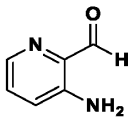
[00496] To a solution of 2-bromonicotinic acid (10 g, 49.5 mmol) in *tert*-butanol (100 mL) was added diphenylphosphoryl azide (10 mL, 49.5 mmol) and triethylamine (7 mL, 49.5 mmol) at room temperature and the reaction mixture was heated at 80 °C for 2 hours. After completion of reaction, the solvent was evaporated under reduced pressure to obtain the crude mass which was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford *tert*-butyl (2-bromopyridin-3-yl)carbamate as a white solid.

Synthesis of tert-butyl (2-formylpyridin-3-yl)carbamate



[00497] To a solution of *tert*-butyl (2-bromopyridin-3-yl)carbamate (8.4 g, 31 mmol) in dry tetrahydrofurane (80 mL) was added 1.6 M solution of *n*-butyl lithium (48 mL, 77 mmol) dropwise at -78 °C under nitrogen atmosphere. After stirring for 1 hour, a solution of piperidine-1-carbaldehyde (4.2 g, 37 mmol) in tetrahydrofuran was added at -78 °C and the reaction mixture was allowed to stirrer at room temperature for 2 hours. After completion of reaction, the reaction mixture was quenched at 0 °C by the slow addition of 1N hydrochloric acid solution. Afterwards, solid sodium carbonate was then added and the solution was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the crude material which was purified by trituration with diethyl ether and n-pentane to afford *tert*-butyl (2-formylpyridin-3-yl)carbamate as a yellow solid

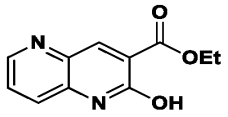
Synthesis of 3-aminopicolinaldehyde



[00498] To a solution of *tert*-butyl (2-formylpyridin-3-yl)carbamate (1 g, 4.5 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (10 mL) and stirred the reaction mixture at room temperature for 5 hours. The progress of reaction was monitored by TLC.

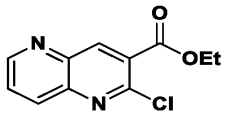
After completion of reaction, solvent was evaporated under rotatory and the residue thus obtained was dissolved into ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by trituration with diethyl ether and *n*-pentane to afford 3-aminopicolinaldehyde as a yellow solid.

Synthesis of *ethyl 2-hydroxy-1,5-naphthyridine-3-carboxylate*



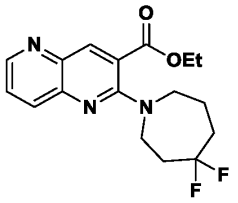
[00499] To a solution of 3-aminopicolinaldehyde (0.5 g, 4 mmol) in ethanol (20 mL) was added diethyl malonate (1.3 mL, 8 mmol) and piperidine (1.4 mL, 16.4 mmol) and the reaction mixture was heated to 80 °C for 12 hours. After completion of reaction, the solvent was evaporated and the crude residue was purified by column chromatography with gradient of 5-10% methanol in dichloromethane to afford ethyl 2-hydroxy-1,5-naphthyridine-3-carboxylate as a brown solid.

Synthesis of ethyl 2-chloro-1,5-naphthyridine-3-carboxylate



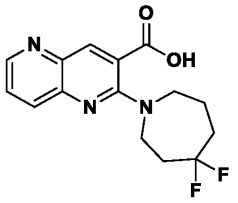
[00500] A mixture of ethyl 2-hydroxy-1,5-naphthyridine-3-carboxylate (0.5 g, 2.2 mmol) and phosphorus oxychloride (5.0 mL) was heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and excess phosphorus oxychloride was distilled out. The crude residue was dissolved into ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude material which was triturated with diethyl ether and n-pentane to obtain ethyl 2-chloro-1,5-naphthyridine-3-carboxylate as a light brown solid.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylate



[00501] To a solution of ethyl 2-chloro-1,5-naphthyridine-3-carboxylate (0.5 g, 2.1 mmol) in *N*,*N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrogen chloride (0.54 g, 3.2 mmol) and dipotassium carbonate (1.2 g, 8.4 mmol). The resulting reaction mixture was heated at 100 °C for 72 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford ethyl 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylic acid



[00502] To a solution of ethyl 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylate (0.5 g, 1.5 mmol) in a mixture of tetrahydrofuran (10 mL) and methanol (10 mL) was added lithium hydroxide (0.07 g, 3 mmol) and water (10 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum. The crude mass was dissolved into water (10 mL), acidified with 1N hydrochloric acid solution and extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylic acid as a light brown solid.

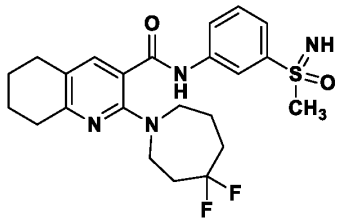
Synthesis of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-1,5-naphthyridine-3-carboxamide

[00503] To a solution of 2-(4,4-difluoroazepan-1-yl)-1,5-naphthyridine-3-carboxylic acid (0.2 g, 0.65 mmol) in dichloromethane (10 mL) was added 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-Oxide Hexafluorophosphate (HATU) (0.38 g, 1 mmol) and 4-Dimethylaminopyridine (0.004 g, 0.03 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, dichloromethane was evaporated under reduced pressure. The crude mass was dissolved into acetonitrile (5.0 mL) and to this, 3-aminobenzenesulfonamide (0.13 g, 0.78 mmol) was added at room temperature and heated at 80 °C for 12 hours. After completion of reaction, acetonitrile was removed under rotatory and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified through reversed phase prep-HPLC to obtain 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-1,5-naphthyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 462.14, found: 462.30

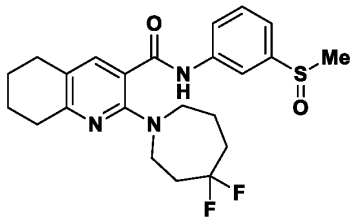
[00504] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.68 (d, J = 4.0, 1.2 Hz, 1H), 8.32 (s, 1H), 8.28 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.88-7.86 (m, 1H), 7.65-7.61 (m, 1H), 7.59-7.55 (m, 2H), 7.41 (s, 2H), 3.78-3.77 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.43-2.36 (m, 2H), 2.07-1.97 (m, 2H), 1.96-1.90 (m, 2H).

Compound 44

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00505] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.15 g, 0.5 mmol) in dichloromethane (10 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.28 g, 0.75 mmol) and 4-Dimethylaminopyridine (0.003 g, 0.025 mmol) at 0 °C and the mixture was stirred at room temperature for 12 hours. After completion of reaction, dichloromethane was evaporated under reduced pressure. The crude mass was dissolved into acetonitrile (5 mL) and to this, 3-(methylsulfinyl) aniline (0.093 g, 0.6 mmol) was added and heated at 80 °C for 12 hours. After completion of reaction, acetonitrile was removed in vacuo. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

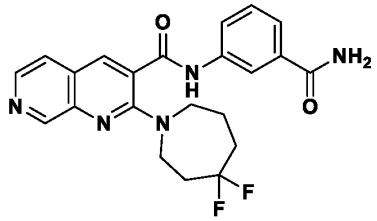
[00506] To a solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.09 g, 0.2 mmol) in Eaton's reagent (2.0 mL) was added sodium azide (0.026 g, 0.4 mmol) at 0 °C, stirred for 15 min at room temperature and heated the mixture at 80 °C for 2 hours. The progress of reaction was monitored by TLC. After completion of reaction, the mixture is quenched with sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexanes to afford 2-(4,4-

difluoroazepan-1-yl)-*N*-(3-(S-methylsulfonimidoyl)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid. MS (ESI): Calcd $[M+H]^+$: 463.20, found: 463.35.

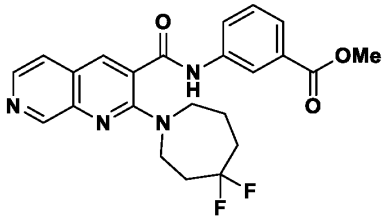
[00507] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.59 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 8.0, 1H), 7.43 (s, 1H), 4.17 (s, 1H), 3.57-3.36 (m, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.04 (s, 3H), 2.70-2.68 (m, 4H), 2.28-2.57 (m, 2H), 1.94-1.90 (m, 2H), 1.80-1.73 (m, 6H).

Compound 45

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamide



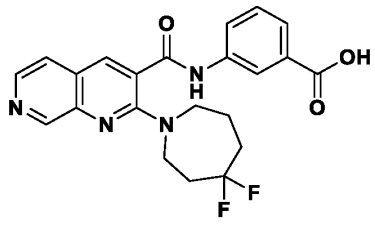
Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate



[00508] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid (0.25 g, 0.81 mmol) in dry dichloromethane (5 mL) was added Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.46 g, 1.2 mmol) and *N,N*-dimethylpyridin-4-amine (0.05 g, 0.41 mmol) was added at 0 °C and reaction mixture was stirred at room temperature for 16 hours. After completion of reaction, solvent was evaporated in vacuo and diluted with acetonitrile (5 mL) and to this, methyl 3-aminobenzoate (0.15 g, 0.98 mmol) was added at room temperature and slowly heated to 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the crude residue was purified

by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate as a white solid.

Synthesis 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoic acid



[00509] To a solution of methyl 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoate (0.15 g, 0.34 mmol) in a mixture of methanol (5 mL), tetrahydrofuran (5 mL) was added a solution of lithium hydroxide (0.072 g, 1.7 mmol) in water (5 mL) at room temperature and stirred for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with water and acidified with 1*N* hydrochloric acid solution and extracted with 10% isopropanol in chloroform. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and the resultant crude material was triturated with diethyl ether and *n*-pentane to afford 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoic acid as a light yellow solid.

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamide

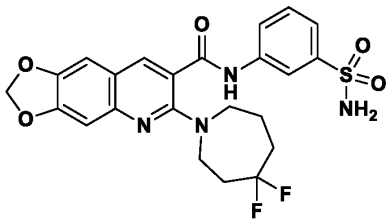
[00510] To a stirred solution of 3-(2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamido)benzoic acid (0.13 g, 0.31 mmol) in *N,N*-dimethylformamide (5 mL) was added ethylbis(propan-2-yl)amine (0.2 g, 1.5 mmol), Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (0.17 g, 0.46 mmol) and ammonium chloride (0.16 g, 3.1 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 16 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material which was purified by flash column chromatography with a gradient of 0-5% methanol in dichloromethane to afford *N*-(3-

carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-1,6-naphthyridine-3-carboxamideas as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 426.17, found: 426.35

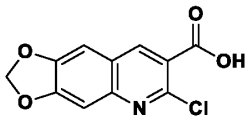
[00511] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 10.88 (s, 1H), 9.00 (s, 1H), 8.37 (s, 1H), 8.35 (d, J = 4 Hz, 1H), 8.18 (s, 1H), 7.97 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.75 (d, J = 4 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.38 (s, 1H), 3.80-3.78 (m, 2H), 3.67 (t, J = 8 Hz, 2H), 2.42-2.39 (m, 2H), 2.03-2.02 (m, 2H), 1.97-1.90 (m, 2H).

Compound 46

Synthesis of 6-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxamide

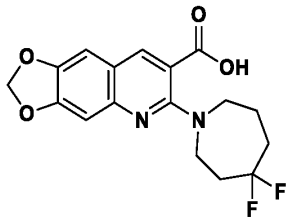


Synthesis of 6-chloro-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid



[00512] To a stirred solution of 6-chloro-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (2 g, 8.5 mmol) in ethanol (35 mL) was added silver nitrate (2.2 g, 13 mmol). To this mixture, a solution of sodium hydroxide (1.7 g, 42.4 mmol) in water (50 mL) was added dropwise. The reaction mixture was stirred at 80 °C for 2 hours. After completion of reaction, the reaction mixture was filtered through celite pad and solvent was removed in vacuo to obtain the crude mass which was diluted with water and acidified with 1*N* hydrochloric acid solution and extracted with ethyl acetate. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material. The crude residue was purified through trituration with diethyl ether and n-pentane to afford 6-chloro-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid as a brown solid.

Synthesis of 6-(4,4-difluoroazepan-1-yl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid



[00513] To a solution of 6-chloro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (0.7 g, 2.8 mmol) in *N,N*-dimethyl formamide (20 mL) was added 4,4-difluoroazepane hydrogen chloride (0.56 g, 4.2 mmol) and potassium carbonate (1.54 g, 11.1 mmol). The mixture was heated at 70 °C for 18 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of the reaction, the crude material was diluted with water followed by treatment with 1*N* hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified through trituration with diethyl ether and n-pentane to afford 6-(4,4-difluoroazepan-1-yl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid as a light brown solid.

Synthesis 6-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxamide

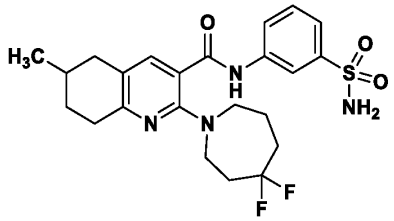
[00514] To a stirred solution of 6-(4,4-difluoroazepan-1-yl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid (0.3 g, 0.86 mmol) in dry dichloromethane (6.0 mL) was added Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (0.488 g, 1.28 mmol) and *N,N*-dimethylpyridin-4-amine (0.052 g, 0.428 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After completion of reaction, solvent was removed under the rotavapour and diluted with acetonitrile (6.0 mL) and 3-aminobenzene-1-sulfonamide (0.18 g, 1mmol) was added to the above solution. The reaction mixture was stirred at 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 6-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-

[1,3]dioxolo[4,5-g]quinoline-7-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 505.14, found: 505.25

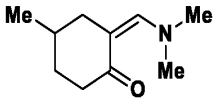
[00515] ^1H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.85-7.82 (m, 1H), 7.56-7.55 (m, 2H), 7.40 (s, 2H), 7.26 (s, 1H), 7.03 (s, 1H), 6.13 (s, 2H), 3.69-3.67 (m, 2H), 3.55 (t, J = 4 Hz, 2H), 2.49-2.37 (m, 2H), 2.00-1.92 (m, 2H), 1.86-1.85 (m, 2H).

Compound 47

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl -N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

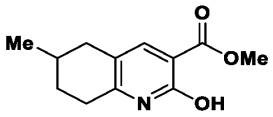


Synthesis of (Z)-2-((dimethylamino)methylene)-5-methylcyclohexan-1-one



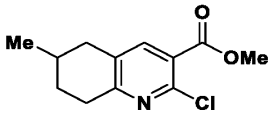
[00516] A mixture of 4-methylcyclohexan-1-one (10 g, 89 mmol) and 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (18.6 g, 107 mmol) was stirred at 70 °C for 18 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed under rotatory to obtain the crude *(Z)*-2-((dimethylamino)methylene)-5-methylcyclohexan-1-one as a brown liquid which was used as such into next step without any purification.

Synthesis of methyl 2-hydroxy-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



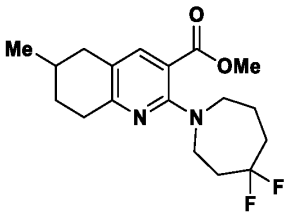
[00517] To the crude (*Z*)-2-((dimethylamino)methylene)-5-methylcyclohexan-1-one (12 g, 72 mmol) in methanol (60 mL) was added methyl 2-cyanoacetate (8.5 g, 86 mmol) and heated the reaction mixture at 80 °C for 12 hours. After completion of reaction, the solvent was removed under rotatory. The crude mass was purified by flash column chromatography with a gradient of 80% ethyl acetate in hexanes to afford methyl 2-hydroxy-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as an off-white solid.

Synthesis of methyl 2-chloro-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



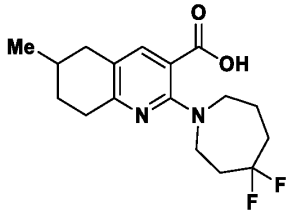
[00518] Methyl 2-hydroxy-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (4 g, 18 mmol) was dissolved into phosphorus oxychloride (40 mL) at room temperature and slowly heated to 130 °C for 12 hours. After completion of reaction, the mixture was then cooled to room temperature and excess of phosphorus oxychloride was distilled out in vacuo. The residue thus obtained was dissolved into ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate and concentrated in vacuum to afford the crude material. The crude material was purified through trituration with diethyl ether and *n*-pentane to afford methyl 2-chloro-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00519] To a solution of 2-chloro-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (2 g, 8.3 mmol) in *N*,*N*-dimethylformamide (20 mL) was added 4,4-difluoroazepane hydrogen chloride (2.15 g, 12.5 mmol) and cesium carbonate (10.9 g, 33.4 mmol). The reaction mixture was heated at 100 °C for 24 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 20% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a pale yellow liquid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00520] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.94 g, 2.78 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added lithium hydroxide (0.47 g, 11 mmol) in water (10 mL) and stirred at room temperature for 12 hours. After completion of reaction, solvent was removed under rotatory and diluted with water, acidified with 1*N* hydrochloric solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

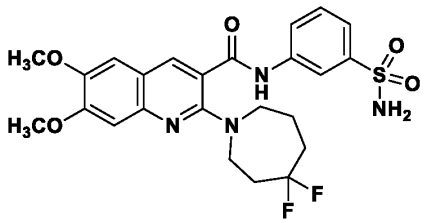
Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00521] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.5g, 1.54 mmol) in dichloromethane (20 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.88 g, 2.3 mmol) and 4-(dimethylamino)pyridine (0.094 g, 0.08 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. After completion of reaction, solvent was evaporated under nitrogen atmosphere and diluted with acetonitrile (20 mL) and to this, 3-aminobenzenesulfonamide (0.32 g, 1.85 mmol) was added and heated to 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, acetonitrile was removed under rotatory. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6-methyl-*N*-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 479.19, found: 479.30

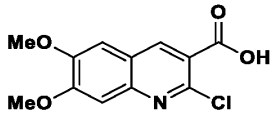
[00522] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 8.30 (s, 1H), 7.78-7.81 (m, 1H), 7.50-7.53 (m, 2H), 7.41 (s, 1H), 7.37 (s, 2H), 3.53-3.62 (m, 2H), 3.36-3.45 (m, 2H), 2.69-2.74 (m, 3H), 2.24-2.30 (m, 3H), 1.81-2.0 (m, 6H), 1.39-1.49 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H).

Compound 48

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

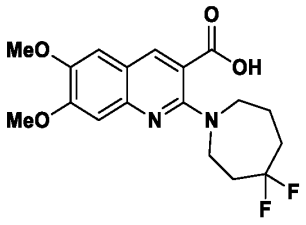


Synthesis of 2-chloro-6,7-dimethoxyquinoline-3-carboxylic acid



[00523] To a stirred solution of 2-chloro-6,7-dimethoxyquinoline-3-carbaldehyde (2 g, 8 mmol) in ethanol (35 mL) was added silver nitrate (2 g, 12 mmol). After 15 min, a solution of sodium hydroxide (2 g, 37.7 mmol) in water (45 mL) was added dropwise and stirred at 80 °C for 2 hours. After completion of reaction, the reaction mixture was filtered through a pad of Celite and filtrate was concentrated under vacuum to obtain a crude mass which was diluted with water and acidified with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material. The crude material was triturated with diethyl ether and *n*-pentane to afford 2-chloro-6,7-dimethoxyquinoline-3-carboxylic acid as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxyquinoline-3-carboxylic acid



[00524] To a solution of 2-chloro-6,7-dimethoxyquinoline-3-carboxylic acid (1 g, 3.7 mmol) in *N*-methyl-2-pyrrolidone (10 mL) was added 4,4-difluoroazepane hydrogen chloride (0.76 g, 5.6 mmol) and potassium carbonate (2.1 g, 14.9 mmol). The reaction mixture was heated at 70 °C for 18 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with cold water followed by treatment with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated. The crude material was triturated with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxyquinoline-3-carboxylic acid as a light brown solid.

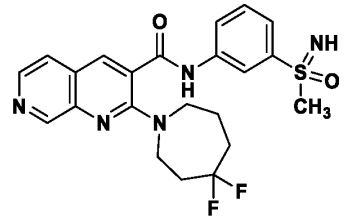
Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00525] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxyquinoline-3-carboxylic acid (0.3 g, 0.8 mmol) in dichloromethane (5 mL) was added Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.47 g, 1.23 mmol) (HATU) and *N,N*-dimethylpyridin-4-amine (DMAP) (0.050 g, 0.41 mmol) was added at 0 °C and stirred at room temperature for 16 hours. After completion of reaction, solvent was evaporated under rotatory and diluted with acetonitrile (5 mL) and to this, 3-aminobenzene-1-sulfonamide (0.17 g, 1 mmol). The reaction mixture was stirred at 70 °C for 16 h. The progress of the reaction was monitored by TLC. After completion the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6,7-dimethoxy-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as an off-white solid. MS (ESI): Calcd $[M+H]^+$: 521.17, found: 521.35.

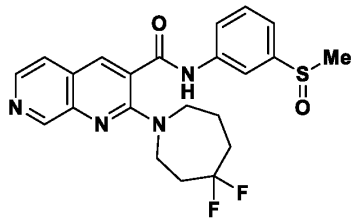
[00526] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 8.34 (s, 1H), 8.15 (s, 1H), 7.84-7.82 (m, 1H), 7.56-7.53 (m, 2H), 7.40 (s, 2H), 7.27 (s, 1H), 7.05 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.70-3.68 (m, 2H), 3.56 (t, J = 4 Hz, 2H), 2.49-2.40 (m, 2H), 2.02-1.96 (m, 2H), 1.87-1.86 (m, 2H)

Compound 49

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,7-naphthyridine-3-carboxamide



Synthesis 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-1,7-naphthyridine-3-carboxamide



[00527] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-1,7-naphthyridine-3-carboxylic acid (0.5 g, 1.6 mmol) in dry dichloromethane (50 mL) was added Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.93 g, 2.4 mmol) and *N,N*-dimethylpyridin-4-amine (0.1 g, 0.8 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. The progress of reaction mixture was monitored by TLC and LCMS. After completion of reaction, solvent was removed in vacuo and diluted with acetonitrile (25 mL) and 3-methanesulfinylaniline (0.3 g, 2 mmol) was added to the above solution at room temperature. The reaction mixture was stirred at 70 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-1,7-naphthyridine-3-carboxamide as a white solid.

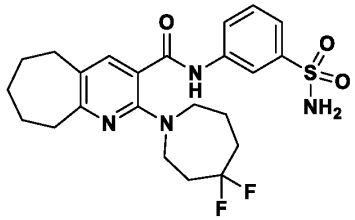
Synthesis 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,7-naphthyridine-3-carboxamide

[00528] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-1,7-naphthyridine-3-carboxamide (0.30 g, 0.675 mmol) in Eaton's Reagent (5 mL) was added sodium azide (0.088 g, 1.35 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 2 hours. The progress of reaction was monitored by TLC and LCMS. After completion of the reaction, the mixture was diluted with water and basified by using sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude compound was purified by flash column chromatography with a gradient of 0-5% methanol in dichloromethane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-1,7-naphthyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 460.16, found: 460.30.

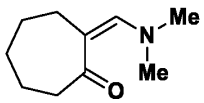
[00529] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.00 (s, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 8.34 (d, J = 4 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 7.75 (d, J = 4 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 4.23 (s, 1H), 3.80-3.77 (m, 2H), 3.65 (t, J = 8 Hz, 2H), 3.07 (s, 3H), 2.43-2.37 (m, 2H), 2.01-2.00 (m, 2H), 1.96-1.90 (m, 2H).

Compound 50

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide



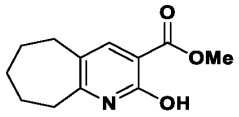
Synthesis of (Z)-2-((dimethylamino)methylene)cycloheptan-1-one



[00530] A solution of cycloheptanone (8.6 g, 77 mmol) in 1-*tert*-butoxy-*N*,*N*,*N*,*N*'-tetramethylmethanediamine (16 g, 77 mmol) was heated at 110 °C for 12 hours. After completion of reaction, the solvent was removed in vacuo to obtain (*Z*)-2-

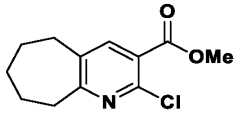
((dimethylamino)methylene)cycloheptan-1-one as a brown liquid which was used as such in the next step without purification.

Synthesis of methyl 2-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylate



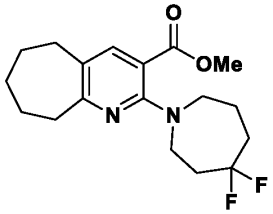
[00531] To a solution of (*Z*)-2-((dimethylamino)methylene)cycloheptan-1-one (12 g, 72 mmol) in methanol (60 mL) was added methyl 2-cyanoacetate (12.7 mL, 143.5 mmol) and slowly heated to 80 °C for 12 hours. After completion of reaction, the solvent was removed in vacuo to obtain the crude solid mass which was purified through trituration with acetonitrile and *n*-pentane to afford methyl 2-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate as white solid.

Synthesis of methyl 2-chloro-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylate



[00532] A solution of methyl 2-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (1 g, 4.5 mmol) in phosphorus oxychloride (10 mL) was heated at 130 °C for 12 hours. After completion of reaction, excess of phosphorus oxychloride was distilled out under rotatory. The crude residue was dissolved into ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by trituration with diethyl ether and *n*-pentane to afford methyl 2-chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate as a white solid.

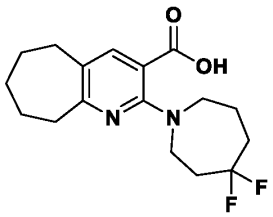
Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylate



[00533] To a solution of methyl 2-chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (1 g, 4.2 mmol) in *N*,*N*-dimethylformamide (15 mL) was added 4,4-

difluoroazepane hydrogen chloride (0.86 g, 5 mmol) and potassium carbonate (2.3 g, 16.7 mmol). The mixture was heated at 100 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexanes to afford methyl 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylic acid



[00534] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (1 g, 3 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added lithium hydroxide (0.25 g, 6 mmol) and water (10 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum. The crude mass was diluted with water, acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude residue which was purified by trituration with diethyl ether and *n*-pentane to afford 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide

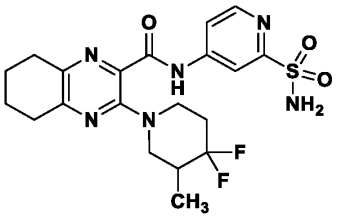
[00535] To a solution of 2-(4,4-difluoroazepan-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carboxylic acid (0.3 g, 0.93 mmol) in dichloromethane (10 mL) was added 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.53 g, 1.4 mmol) and 4-Dimethylaminopyridine (0.006 g, 0.05

mmol) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, solvent was evaporated under reduced pressure. The resultant crude mass was dissolved into acetonitrile (10 mL) and to this solution, 3-aminobenzenesulfonamide (0.19 g, 1.1 mmol) was added and heated at 80 °C for 12 hours. After completion of reaction, acetonitrile was removed in vacuo and the crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered and filtrate was concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 479.19, found: 479.25.

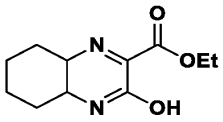
[00536] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.30 (s, 1H), 7.80-7.78 (m, 1H), 7.52-7.46 (m, 2H), 7.46 (s, 1H), 7.37 (s, 2H), 3.59-3.58 (m, 2H), 3.39 (t, J = 6.0 Hz, 2H), 2.87-2.84 (m, 2H), 2.70-2.69 (m, 2H), 2.30-2.26 (m, 2H), 1.97-1.94 (m, 2H), 1.80-1.79 (m, 4H), 1.59-1.57 (m, 4H).

Compound 51

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide

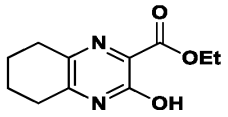


Synthesis of ethyl 3-hydroxy-4a,5,6,7,8,8a-hexahydroquinoxaline-2-carboxylate



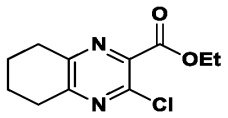
[00537] A solution of cyclohexane-1,2-diamine (230 mg, 2 mmol) and diethyl 2-oxomalonate (305 µL, 2 mmol) in ethanol (10 mL) was stirred at 70 °C for 18 hours. The solvent was removed in vacuo and the product was used directly in the next step.

Synthesis of ethyl 3-hydroxy-5,6,7,8-tetrahydroquinoxaline-2-carboxylate



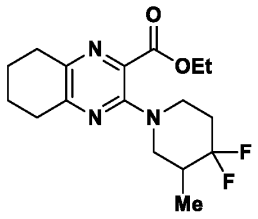
[00538] Ethyl 3-hydroxy-4a,5,6,7,8,8a-hexahydroquinoxaline-2-carboxylate neat was heated to 110 °C for 72 hours under air then purified by flash column chromatography using a Combiflash with a gradient of 0-50% ethyl acetate in hexanes to afford ethyl 3-hydroxy-5,6,7,8-tetrahydroquinoxaline-2-carboxylate as a yellow solid.

Synthesis of ethyl 3-chloro-5,6,7,8-tetrahydroquinoxaline-2-carboxylate



[00539] A mixture of ethyl 3-hydroxy-5,6,7,8-tetrahydroquinoxaline-2-carboxylate (400 mg, 1.8 mmol) and phosphorous oxychloride (7 mL) was slowly heated to 110 °C for 72 hours. After completion of the reaction, the reaction mixture was quenched with ice-cold water and saturated sodium bicarbonate solution, then extracted with dichloromethane. The organic layers were combined then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography using a Combiflash with a gradient of 0-50% ethyl acetate in hexanes to afford ethyl 3-chloro-5,6,7,8-tetrahydroquinoxaline-2-carboxylate as a yellow oil.

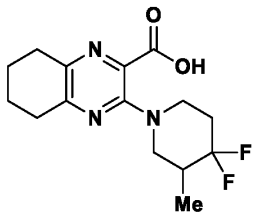
Synthesis of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxylate



[00540] To a solution of ethyl 3-chloro-5,6,7,8-tetrahydroquinoxaline-2-carboxylate (135 mg, 0.56 mmol) and 4,4-difluoro-3-methylpiperidine hydrogen chloride (97 mg, 0.56 mmol) in *N,N*-dimethylformamide (4 mL), potassium carbonate (390 mg, 2.8 mmol) was added at room temperature. The reaction mixture was stirred at 70 °C for 72 hours. The progress of the

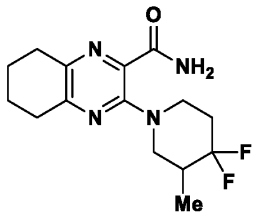
reaction was monitored by TLC and LCMS. After completion, the reaction mixture was diluted with water and hydrochloric acid 1 N then extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford 3-chloro-5,6,7,8-tetrahydroquinoxaline-2-carboxylic acid as a yellow oil.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxylic acid



[00541] To a stirred solution of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxylate (0.94 g, 0.28 mmol) in methanol (2.8 mL) and tetrahydrofuran (12 mL) was added 1 N sodium hydroxide (2.8 mL). The reaction mixture was stirred at room temperature for 18 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, solvent was removed under rotatory and diluted with water, then acidified with 1 N hydrochloric acid solution and extracted with dichloromethane. The organic layers were combined, dried with sodium sulfate, filtered and concentrated to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxylic acid as a light brown powder.

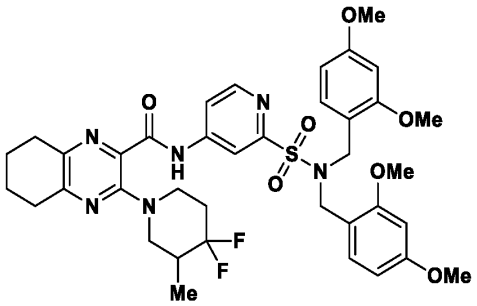
Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide



[00542] To a stirred solution of 3-(4,4-Difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxylic acid (86 mg, 0.28. mmol), in dichloromethane (5 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide

hexafluorophosphate (HATU) (0.16 g, 0.41 mmol) and ammonium carbonate (0.13 g, 1.4 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was diluted with water and extracted dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude material. The crude residue was purified by flash column chromatography using a Combiflash with a gradient of 0-50% ethyl acetate in hexanes to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide as a light yellow powder.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide



[00543] 3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide (36 mg, 0.116 mmol), 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (62 mg, 0.116 mmol), cesium carbonate (76 mg, 0.23 mmol), and BrettPhos Pd G3 (21 mg, 0.023 mmol) were added to a flame dried round bottom flask and capped. The reaction vessel was evacuated and the atmosphere was replace with nitrogen. Then, degassed anhydrous dioxane (3 mL) was added to the reaction vessel and the mixture was stirred at 100 °C for 18 hours. Dioxane was removed in vacuo and the crude mixture was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide as a yellow oil.

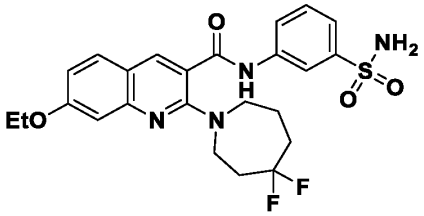
Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide

[00544] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide (27 mg, 0.1 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (155 µL). The reaction mixture was stirred for 18 hours then the volatiles were removed in vacuo. Volatiles were removed in vacuo and the resulting crude mixture was diluted with water and acetonitrile then purified using reversed-phase HPLC with a gradient of 5-95% acetonitrile in water to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide as a white powder. LRMS (ESI): Calcd $[M+H]^+$: 467.17, found: 466.9

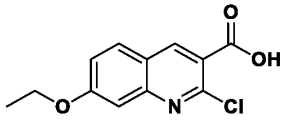
[00545] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 7.82 (d, *J* = 5.6 Hz, 1H), 3.69 – 3.54 (m, 2H), 3.04 – 2.95 (m, 1H), 2.79 – 2.70 (m, 1H), 2.69 – 2.57 (m, 4H), 2.08 – 1.82 (m, 3H), 1.76 – 1.61 (m, 4H), 0.79 (d, *J* = 6.8 Hz, 3H).

Compound 52

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-ethoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide



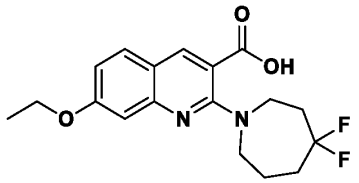
Synthesis of 2-chloro-7-ethoxyquinoline-3-carboxylic acid



[00546] To a solution of silver nitrate (0.54 g, 3.2 mmol) in water (13 mL) was added sodium hydroxide (0.42 g, 10.6 mmol) and mixture was stirred for 30 min at room temperature. A solution of 2-chloro-7-ethoxyquinoline-3-carbaldehyde (0.5 g, 2.12 mmol) in ethanol (10 mL) was added dropwise then the mixture was heated to 80 °C and stirred for 5 hours. After reaction completion, the reaction mixture was filtered through Celite and the solvent was removed in

vacuo. The residue was diluted with water, acidified by 1M hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered, then concentrated to afford 2-chloro-7-ethoxyquinoline-3-carboxylic acid as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-ethoxyquinoline-3-carboxylic acid



[00547] To a solution of 2-chloro-7-ethoxyquinoline-3-carboxylic acid (0.4 g, 1.59 mmol) in 1-methylpyrrolidin-2-one (10 mL) was added potassium carbonate (0.88 g, 6.4 mmol) and 4,4-difluoroazepane hydrochloride (0.32 g, 2.4 mmol). The reaction mixture was stirred at 110 °C for 16 hours. After reaction completion, the reaction mixture was quenched with cold water, acidified using 1M hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered, concentrated to afford product of 2-(4,4-difluoroazepan-1-yl)-7-ethoxyquinoline-3-carboxylic acid as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-ethoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

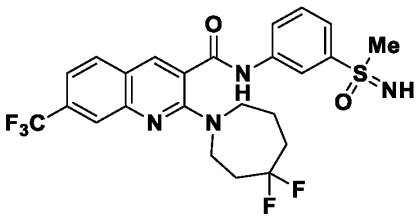
[00548] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-ethoxyquinoline-3-carboxylic acid (0.2 g, 0.57 mmol) in dichloromethane (10 mL) was added HATU (0.33 g, 0.86 mmol) and *N*,*N*-dimethylpyridin-4-amine (0.35 g, 0.29 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo then diluted with acetonitrile (5 mL). To this solution was added 3-aminobenzene-1-sulfonamide (0.98 g, 0.57 mmol) was added. The reaction mixture was heated at 80 °C for 18 hours. After reaction completion, the reaction mixture was extracted with ethyl acetate and water. The organic layers were dried over sodium sulfate, filtered, then concentrated to afford crude product which was purified by reversed phase Prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-ethoxy-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a white solid. Yield: 0.14 g, 49%; LRMS (ESI): Calcd $[M+H]^+$: 505.17, found: 505.25.

[00549] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.31 (s, 1H), 8.23 (s, 1H), 7.86-7.83 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.56-7.53 (m, 2H), 7.40 (s, 2H), 7.00 (d, J = 2.4 Hz ,1H), 6.92 (dd, J = 8.0 Hz, J = 4.0 Hz ,1H), 4.18-4.13 (m, 2H), 3.74-3.72 (m, 2H), 3.59 (t, J =

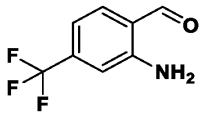
12.0 Hz, 2H), 2.41-2.37 (m, 2H), 2.00-1.98 (m, 2H), 1.95-1.87 (m, 2H), 1.38 (t, J = 12.0 Hz, 3H).

Compound 53

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-7-(trifluoromethyl)quinoline-3-carboxamide

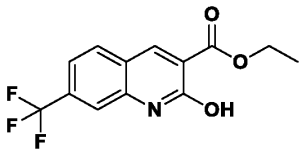


Synthesis of 2-amino-4-(trifluoromethyl)benzaldehyde



[00550] To a stirred solution of 2-nitro-4-(trifluoromethyl)benzaldehyde (2.3 g, 10.5 mmol) in ethanol (25 mL) was added iron powder (6.1 g, 105 mmol). To this mixture, concentrated hydrochloric acid (0.2 mL) was added dropwise. The reaction mixture was stirred for 2 hours under reflux condition. After reaction completion, the reaction mixture was filtered through Celite, concentrated, diluted with water, then extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate then concentrated. The residue was triturated with pentane to afford 2-amino-4-(trifluoromethyl)benzaldehyde as pale-yellow solid.

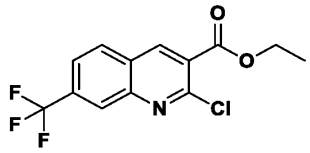
Synthesis of ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate



[00551] To a stirred solution of 2-amino-4-(trifluoromethyl)benzaldehyde (1.6 g, 8.5 mmol) in ethanol (30 mL) was added diethyl malonate (13.5 g, 84.6 mmol) and piperidine (4.2 mL, 42.3 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 hours. After reaction completion, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, concentrated, then

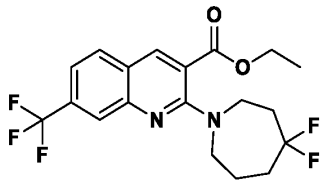
triturated with diethyl ether to afford ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate as an off-white solid.

Synthesis of ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate



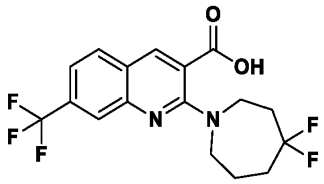
[00552] Ethyl 2-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate (0.7 g, 2.5 mmol) was dissolved into phosphorus oxychloride (7 mL, 75 mmol) at room temperature and heated to 110 °C for 12 hours. The reaction mixture was cooled to room temperature and excess phosphorus oxychloride was distilled out. The residue was dissolved into ethyl acetate and washed with an aqueous sodium bicarbonate solution. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate, then concentrated in vacuo to afford the residue which was triturated with diethyl ether and pentane to afford ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate as a brown oil.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate



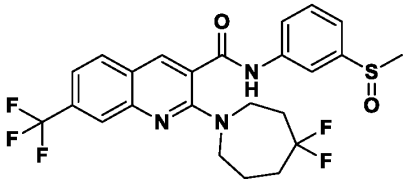
[00553] To a solution of ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate (0.6 g, 2 mmol) in *N*,*N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrochloride (0.5 g, 3 mmol) and potassium carbonate (1.1 g, 7.9 mmol). The mixture was heated at 80 °C for 16 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by silica gel column chromatography with a gradient of 20% ethyl acetate in hexane to afford ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate as yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid



[00554] To a stirred solution of ethyl 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylate (0.6 g, 1.5 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.21 g, 6 mmol) in water (10 mL). The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the solvent was removed under reduced pressure. The residue was diluted with ice cold water followed by acidification with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue triturated with pentane and diethyl ether to afford 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid as a brownish solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-7-(trifluoromethyl)quinoline-3-carboxamide



[00555] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethyl)quinoline-3-carboxylic acid (0.3 g, 0.80 mmol) in dichloromethane (15 mL) was added HATU (0.46 g, 1.2 mmol) and 4-(dimethylamino) pyridine (0.05 g, 0.4 mmol) at 0 °C. The mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo under nitrogen atmosphere and diluted with acetonitrile (10 mL). To this solution, 3-methanesulfinylaniline (0.15 g, 0.96 mmol) was added, heated to 80 °C, and stirred for 12 hours. After reaction completion, the solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 40%-50% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-7-(trifluoromethyl)quinoline-3-carboxamide as a white solid.

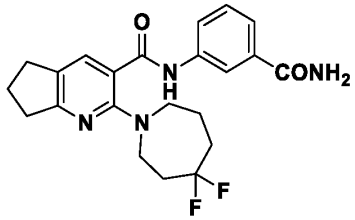
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-7-(trifluoromethyl)quinoline-3-carboxamide

[00556] To a solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-methanesulfinylphenyl)-7-(trifluoromethyl)quinoline-3-carboxamide (0.13 g, 0.25 mmol) in Eaton's reagent (3 mL) was added sodium azide (0.033 g, 0.51 mmol). The mixture was heated at 50 °C for 2 hours. After reaction completion, the reaction mixture was diluted with ice cold water and quenched with saturated sodium carbonate solution. The solution was extracted with ethyl acetate and the organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-7-(trifluoromethyl)quinoline-3-carboxamide as pale yellow solid. Yield: 0.018 g, 13%; LRMS (ESI): Calcd $[M+H]^+$: 525.15, found: 525.15.

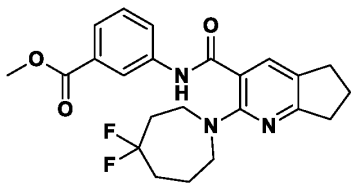
[00557] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 8.48 (s, 1H), 8.35 (t, J = 1.6 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.92 (br s, 1H), 7.70-7.68 (m, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.4, 1.6 Hz, 1H), 4.23 (br s, 1H), 3.81-3.78 (m, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.07 (s, 3H), 2.43-2,42 (m, 2H), 2.09-1.97 (m, 2H), 1.92-1.91 (m, 2H).

Compound 54

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide`



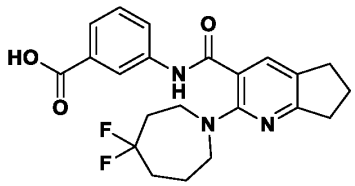
Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamido)benzoate



[00558] To a solution of 2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylic acid (0.20 g, 0.66 mmol) in dichloromethane (2 mL) was

added HATU (0.36 g, 0.96 mmol) and 4-dimethylaminopyridine (0.041 g, 0.33 mmol) at 0 °C. The mixture was stirred under nitrogen atmosphere at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was diluted with acetonitrile (2 mL). To this solution, methyl 3-aminobenzoate (0.12 g, 0.79 mmol) was added and the mixture was heated to 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo. The residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford methyl 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamido)benzoate as a light yellow solid.

Synthesis of 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamido)benzoic acid



[00559] To a solution of methyl 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamido) benzoate (0.15 g, 0.35 mmol) in tetrahydrofuran (1.5 mL) and methanol (1.5 mL) was added lithium hydroxide (0.06 g, 1.4 mmol) in water (1.5 mL) then stirred at room temperature for 12 hours. After reaction completion, the solvent was removed under reduced pressure. The residue was diluted with water, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamido)benzoic acid as an off-white solid.

Synthesis of N-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide

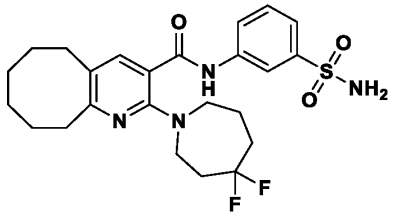
[00560] To a solution of 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamido) benzoic acid (0.10 g, 0.24 mmol) in *N,N*-dimethylformamide (1 mL) was added ammonium chloride (0.13 g, 2.4 mmol), *N,N*-diisopropylethylamine (0.1 mL, 0.72 mmol) and HATU (0.137 g, 0.36 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the

reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexanes to afford *N*-(3-carbamoylphenyl)-2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide as a white solid. Yield: 0.023 g, 23%; LRMS (ESI): Calcd $[M+H]^+$: 415.19, found: 415.30.

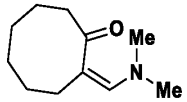
[00561] ^{1}H NMR (400 MHz, DMSO-d_6): 10.39 (s, 1H), 8.16 (s, 1H), 7.91 (brs, 1H), 7.81 (d, J = 8 Hz, 1H), 7.56-7.54 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.34 (br s, 1H), 3.59-3.56 (m, 2H), 3.40 (t, 12 Hz, 2H), 2.81 (t, J = 7.6 Hz, 4H), 2.35-2.27 (m, 2H), 2.08-2.02 (m, 2H), 2.00-1.95 (m, 2H), 1.91-1.81 (m, 2H).

Compound 55

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide

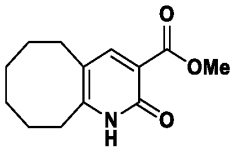


Synthesis of (Z)-2-((dimethylamino)methylene)cyclooctan-1-one



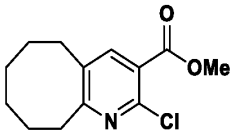
[00562] To a stirred solution of cyclooctanone (5 g, 39.6 mmol) in toluene (25 mL), [(tert-butoxy)(dimethylamino)methyl]dimethylamine (7.6 g, 43.6 mmol) was added at room temperature. The resulting mixture was heated at 100 °C for 18 hours. Progress of the reaction was monitored by TLC. Afterwards, the reaction mixture was concentrated under vacuum to afford the crude (*Z*)-2-((dimethylamino)methylene)cyclooctan-1-one as a brown liquid. The crude product was used in the next step without purification.

Synthesis of methyl 2-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate



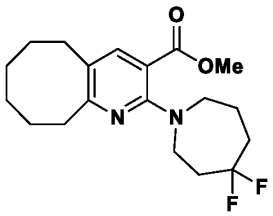
[00563] To a stirred solution of (*Z*)-2-((dimethylamino)methylene)cyclooctan-1-one (7.0 g, 38.7 mmol) in methanol (50 mL), methyl 2-cyanoacetate (4.6 g, 46.4 mmol) was added dropwise and the resulting mixture was heated at 80 °C for 18 hours. After completion of reaction, the reaction mixture was concentrated under vacuum to obtain the crude product which was suspended in acetonitrile and stirred at room temperature for 10 minutes. The resulting precipitate formed was filtered and washed with acetonitrile to obtain methyl 2-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate as a white solid.

Synthesis of methyl 2-chloro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate



[00564] A solution of phosphoroyl trichloride (50 mL) and methyl 2-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate (5.0 g, 21.3 mmol) was heated at 110 °C for 18 hours. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under vacuum to remove excess of phosphoryl trichloride and the residue was mixed with ice-cold water, neutralized with saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the crude product. The residue was purified by flash column chromatography with a gradient of 20-30 % ethyl acetate in hexane to afford methyl 2-chloro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate as a yellow oil.

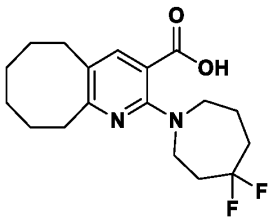
Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate



[00565] To a stirred solution of methyl 2-chloro-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate (2 g, 7.9 mmol) in *N,N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrogen chloride (2 g, 11.8 mmol) and potassium carbonate (5.5 g, 39.4 mmol) were added. The resulting mixture was heated at 100 °C for 24

hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum and crude residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylic acid



[00566] To a stirred solution of methyl 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate (1.0 g, 2.84 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL), aqueous solution of lithium hydroxide (0.27 g, 11.3 mmol) in water (10 mL) was added. The resulting mixture was stirred at room temperature for 24 hours. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under vacuum to remove the organic solvents. The resulting residue was diluted with water, neutralized with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude residue, which was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide

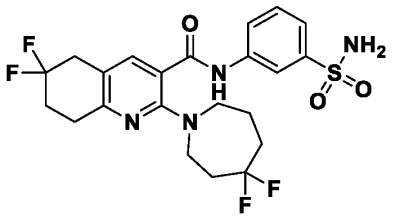
[00567] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylic acid (0.4 g, 1.18 mmol) in dichloromethane (40 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.67 g, 1.77 mmol) and *N,N*-dimethylpyridin-4-amine (0.07 g, 0.59 mmol) at 0-5 °C. The resulting mixture was stirred at room temperature for 18

hours. After consumption of starting material, the reaction mixture was evaporated in vacuo to remove the dichloromethane and the resulting residue was dissolved with acetonitrile (40 mL) and to this mixture, 3-aminobenzene-1-sulfonamide (0.24 g, 1.4 mmol) was added and heated at 80 °C for 18 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the crude product. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide as an off-white solid. LRMS (ESI): Calcd $[M+H]^+$: 493.21, found: 493.35.

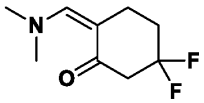
[00568] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.31 (s, 1H), 7.83-7.80 (m, 1H), 7.53-7.51 (m, 2H), 7.46 (s, 1H), 7.38 (s, 2H), 3.60-3.59 (m, 2H), 3.42-3.39 (m, 2H), 2.78 (t, J = 5.60 Hz, 2H), 2.69-2.67 (m, 2H), 2.33-2.27 (m, 2H), 1.98-1.93 (m, 2H), 1.83-1.82 (m, 2H), 1.68-1.62 (m, 4H), 1.40-1.36 (m, 4H).

Compound 56

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

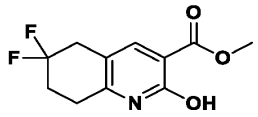


Synthesis of (Z)-2-((dimethylamino)methylene)-5,5-difluorocyclohexan-1-one



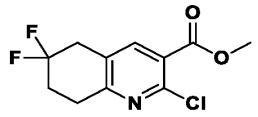
[00569] A mixture of 4,4-difluorocyclohexan-1-one (10 g, 74.6 mmol) and 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (15.6 g, 89.5 mmol) was stirred at 70 °C for 18 hours. After reaction completion, the solvent was removed under reduced pressure to obtain crude (*Z*)-2-((dimethylamino)methylene)-5,5-difluorocyclohexan-1-one as brown liquid which was used in the next step without further purification.

Synthesis of methyl 6,6-difluoro-2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate



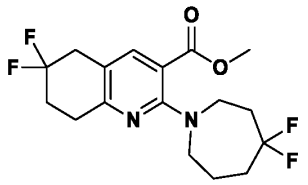
[00570] To the crude (*Z*)-2-((dimethylamino)methylene)-5,5-difluorocyclohexan-1-one (12 g, 63.4 mmol) in methanol (60 mL) was added methyl 2-cyanoacetate (7.5 g, 76 mmol) and the mixture was heated at 80 °C for 12 hours. After reaction completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography with a gradient of 80% ethyl acetate in hexane to afford methyl 6,6-difluoro-2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate as an off-white solid.

Synthesis of methyl 2-chloro-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00571] Methyl 6,6-difluoro-2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxylate (3 g, 12.3 mmol) was dissolved into phosphorus oxychloride (30 mL) at room temperature, heated to 110 °C, and stirred for 12 hours. After completion, the mixture was then cooled to room temperature and excess phosphorus oxychloride was distilled out. The residue was dissolved into ethyl acetate and washed with aqueous sodium bicarbonate solution. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with diethyl ether and pentane to afford methyl 2-chloro-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

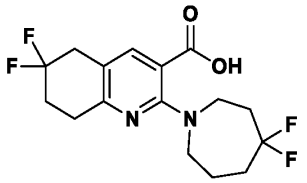
Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00572] To a solution of methyl 2-chloro-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylate (2 g, 7.6 mmol) in 1-methylpyrrolidin-2-one (5 mL) was added 4,4-difluoroazepane hydrochloride (2 g, 11.5 mmol). Ethylbis(propan-2-yl)amine (2 mL, 30.56 mmol) was then added dropwise. The mixture was heated at 130 °C for 24 hours. After reaction

completion, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered, then concentrated. The residual was purified by flash column chromatography with a gradient of 20% ethyl acetate in hexane to afford methyl 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00573] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7, 8-tetrahydroquinoline-3-carboxylate (0.8 g, 2.2 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added lithium hydroxide (0.37 g, 8.9 mmol) in water (10 mL) and stirred at 60 °C for 24 hours. After reaction completion, the solvent was removed under reduced pressure, diluted with water, acidified with 1*N* hydrochloric acid solution, then extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and *n*-pentane to 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

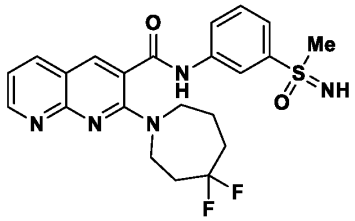
[00574] To a solution of 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.5 g, 1.4 mmol) in dichloromethane (10 mL) was added HATU (0.82 g, 2.17 mmol) and 4-dimethylaminopyridine (0.09 g, 0.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo under nitrogen atmosphere and the residue was dissolved with acetonitrile (10 mL). To this solution was added 3-aminobenzenesulfonamide (0.3 g, 1.7 mmol) and heated to 80 °C for 12 hours. After reaction completion, the solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residual was purified by flash column chromatography with a gradient

of 40% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-6,6-difluoro-*N*-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. Yield: 0.025 g, 3%; LRMS (ESI): Calcd $[M+H]^+$: 501.16, found: 501.25.

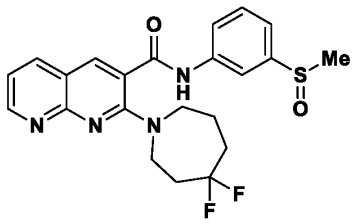
[00575] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.28 (s, 1H), 7.81-7.79 (m, 1H), 7.54-7.51 (m, 3H), 7.39 (br s, 2H), 3.60-3.59 (m, 2H), 3.41 (t, J = 6.0 Hz, 2H), 3.22-3.19 (m, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.38-2.27 (m, 4H), 1.99-1.91 (m, 2H), 1.83-1.82 (m, 2H).

Compound 57

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,8-naphthyridine-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-1,8-naphthyridine-3-carboxamide



[00576] To a stirred suspension of 2-(4,4-difluoroazepan-1-yl)-1,8-naphthyridine-3-carboxylic acid (0.4 g, 1.3 mmol) in dichloromethane (30 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.74 g, 2 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP) (0.079 g, 0.065 mmol) were added sequentially at 0-5 °C and the resulting reaction mixture was stirred at room temperature for 18 hours. After completion of reaction, the solvent was evaporated and the resulting crude residue was dissolved into acetonitrile (30 mL) and to this, 3-(methylsulfinyl)aniline (0.24 g, 1.6 mmol) was added and slowly refluxed for 18 hours. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate

and evaporated under vacuum to afford the crude 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-1,8-naphthyridine-3-carboxamide as a light yellow color viscous oil which was used as such into next step without purification.

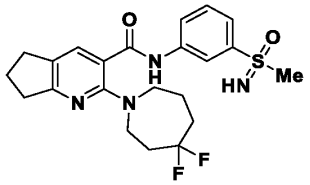
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-1,8-naphthyridine-3-carboxamide

[00577] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-methanesulfinylphenyl)-1,8-naphthyridine-3-carboxamide (0.25 g, 0.56 mmol) in Eaton's reagent (10 wt% phosphorus pentoxide solution in methanesulfonic acid), sodium azide (0.073 g, 1.1 mmol) was added at 0 °C and the reaction mixture was slowly warmed to room temperature and then heated to 50 °C for 2 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured over crushed ice, neutralized with saturated aqueous solution of sodium carbonate (pH~7), extracted with ethyl acetate, and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to afford the crude product which was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-1,8-naphthyridine-3-carboxamide as a pale yellow solid. LRMS (ESI): Calcd $[M+1]^+$. 460.16, found: 460.10

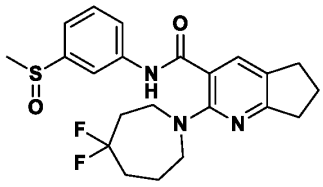
[00578] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.85-8.83 (m, 1H), 8.41 (s, 1H), 8.33-8.29 (m, 1H), 8.33-8.26 (m, 1H), 7.98-7.96 (m, 1H), 7.69-7.67 (m, 1H), 7.69-7.63 (m, 1H), 7.33-7.30 (m, 1H), 4.32 (brs,1H), 3.82-3.79 (m, 2H), 3.66-3.63 (m, 2H), 3.07 (s, 3H), 2.42-2.38 (m, 2H), 2.00-1.97 (m, 2H), 1.92-1.90 (m, 2H).

Compound 58

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide



Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfinyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide



[00579] To a solution of 3-(2-(4,4-difluoroazepan-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamido)benzoic acid (0.15 g, 0.35 mmol) in dichloromethane (4 mL) was added HATU (0.2 g, 0.53 mmol) and 4-dimethylaminopyridine (0.004 g, 0.035 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo under nitrogen atmosphere and the residue was dissolved with acetonitrile (1.5 mL). To this solution was added 3-(methylsulfinyl) aniline (0.067 g, 0.42 mmol) then heated to 80 °C for 12 hours. After reaction completion, the mixture was concentrated. The residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide as a light yellow solid.

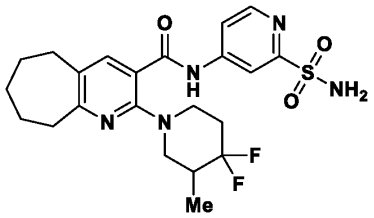
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(S-methylsulfonimidoyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide

[00580] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(methylsulfinyl)phenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide (0.10 g, 0.23 mmol) in Eaton's Reagent (4.6 mL) was added sodium azide (0.030 g, 0.46 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 2 hours. After reaction completion, the reaction mixture was diluted with water, basified using sodium carbonate and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexanes to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(*S*-methylsulfonimidoyl)phenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxamide as an off-white solid. Yield: 0.031 g, 30%; LRMS (ESI): Calcd $[M+H]^+$: 449.18, found: 449.25.

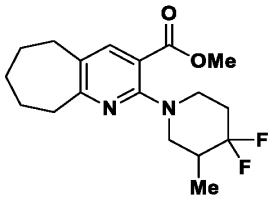
[00581] ^{1}H NMR (400 MHz, DMSO-d_6): 10.61 (s, 1H), 8.34 (brs, 1H), 7.91 (d, J = 80 Hz, 1H), 7.63-7.53 (m, 3H), 4.19 (s, 1H), 3.59-3.56 (m, 2H), 3.38 (t, J = 6.0 Hz, 2H), 3.04 (s, 3H), 2.81 (t, J = 7.2 Hz, 4H), 2.32-2.28 (m, 2H), 2.08-2.04 (m, 2H), 2.02-1.94 (m, 2H), 1.80-1.83 (m, 2H).

Compound 59

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide

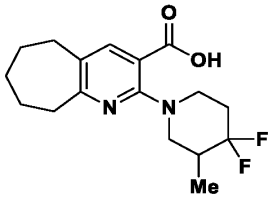


Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylate



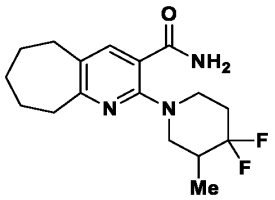
[00582] To a solution of methyl 2-chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (0.50 g, 2.1 mmol) in *N*,*N*-dimethylformamide (2.5 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.43 g, 2.5 mmol) and potassium carbonate (1.15 g, 8.4 mmol). The mixture was heated at 100 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was triturated with diethyl ether and n-pentane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-*5H*-cyclohepta[b]pyridine-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylic acid



[00583] To a solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (0.38 g, 1.1 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) was added lithium hydroxide (0.13 g, 5.5 mmol) and water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum, diluted with water, acidified with 1*N* hydrogen chloride solution then extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, then filtered. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified through trituration with diethyl ether and n-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylic acid as a white solid.

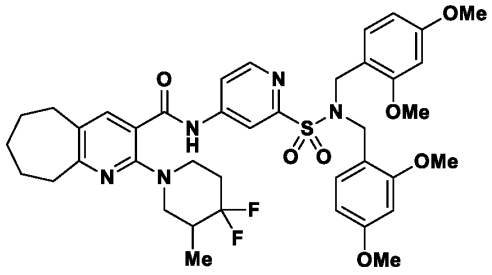
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide



[00584] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxylic acid (0.29 g, 0.84 mmol) in *N*,*N*-dimethylformamide (3 mL) was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.48 g, 1.2 mmol) and *N*,*N*-diisopropylethylamine (0.73 mL, 4.2 mmol) and ammonium chloride (0.44 g, 8.4 mmol) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude residue was triturated with diethyl ether and n-

pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide



[00585] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carboxamide (0.12 g, 0.37 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.23 g, 0.44 mmol), cesium carbonate (0.24 g, 0.74 mmol) and BrettPhos Pd G3 (0.03 g, 0.03 mmol) under nitrogen atmosphere and heated the mixture at 100 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was evaporated then the crude compound was diluted with extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide

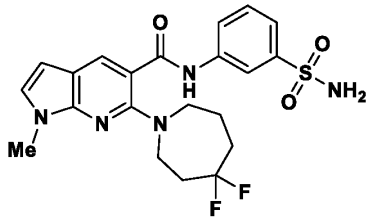
[00586] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide (0.16 g, 0.2 mmol) in dichloromethane (1.6 mL) was added trifluoroacetic acid (0.8 mL) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and the residue obtained was dissolved in ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with brine solution, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material which was purified by

flash column chromatography with a gradient of 30-35% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carboxamide as a white solid. LRMS (ESI): Calcd $[M+H]^+$: 480.19, found: 480.05.

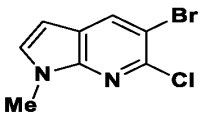
[00587] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 1.2 Hz, 1H), 7.80-7.79 (m, 1H), 7.63 (s, 1H), 7.45 (s, 2H), 3.60 (t, J = 13.6 Hz, 2H), 3.06 (t, J = 10.8 Hz, 1H), 2.92-2.89 (m, 2H), 2.83 (t, J = 11.2 Hz, 1H), 2.80-2.74 (m, 2H), 2.12-2.07 (m, 2H), 1.95-1.82 (m, 3H), 1.59-1.58 (m, 4H), 0.89 (d, J = 6.8 Hz, 3H).

Compound 60

Synthesis of 6-(4,4-difluoroazepan-1-yl)-1-methyl-N-(3-sulfamoylphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxamide

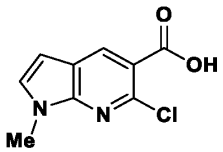


Synthesis of 5-bromo-6-chloro-1-methyl-1H-pyrrolo[2,3-b]pyridine



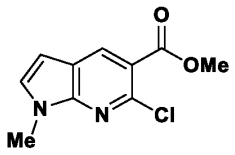
[00588] To a solution of 5-bromo-6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (4.5 g, 20 mmol) in *N*,*N*-dimethylformamide (45 mL) was added potassium carbonate (6.9 g, 50 mmol) and methyl iodide (1.5 mL, 24.0 mmol) at 0 °C under nitrogen atmosphere. The mixture was heated at 80 °C for 12 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and the brown precipitate was filtered and washed with n-pentane to afford 5-bromo-6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine as a brown solid.

Synthesis of 6-chloro-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid



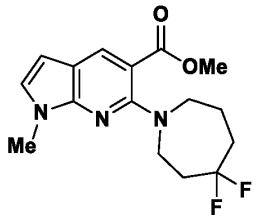
[00589] To a solution of 5-bromo-6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.0 g, 8.0 mmol) in dry THF (20 mL) was added n-BuLi (6.0 mL, 9.6 mmol, 1.6 M in hexane) at -78 °C under nitrogen atmosphere and stirred for 1 hour. Dry ice (2.0 g) was added at -78 °C and the mixture was allowed to stir at room temperature for 5 hours. The reaction mixture was quenched by the addition of 1*N* hydrochloric acid. The solution was extracted with ethyl acetate and combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material which was triturated with diethyl ether and n-pentane to afford 6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid as an off-white solid.

Synthesis of methyl 6-chloro-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylate



[00590] To a solution of 6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid (1.6 g, 7.2 mmol) in *N*,*N*-dimethylformamide (16 mL) was added potassium carbonate (6.8 g, 18 mmol) and methyl iodide (0.7 mL, 10.8 mmol) at 0 °C under nitrogen atmosphere and the mixture was heated at 80 °C for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate as a light yellow solid.

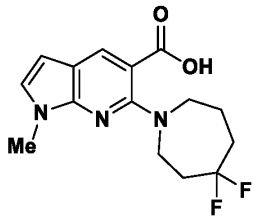
Synthesis of methyl 6-(4,4-difluoroazepan-1-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylate



[00591] To a solution of methyl 6-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (1.4 g, 6.2 mmol) in *N*,*N*-dimethylformamide (14 mL) was added 4,4-difluoroazepane hydrochloride (1.59 g, 9.3 mmol) and potassium carbonate (4.2 g, 31.0 mmol).

The mixture was heated at 100 °C for 24 hours under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate then filtered and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford methyl 6-(4,4-difluoroazepan-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate as a yellow viscous oil.

Synthesis of 6-(4,4-difluoroazepan-1-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid



[00592] To a solution of methyl 6-(4,4-difluoroazepan-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (0.8 g, 2.5 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) was added lithium hydroxide (0.2 g, 5 mmol) and water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated under vacuum, diluted with water, acidified with 1*N* hydrochloric acid then extracted with ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified through trituration with diethyl ether and n-pentane to afford 6-(4,4-difluoroazepan-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid as a white solid.

Synthesis of 6-(4,4-difluoroazepan-1-yl)-1-methyl-N-(3-sulfamoylphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxamide

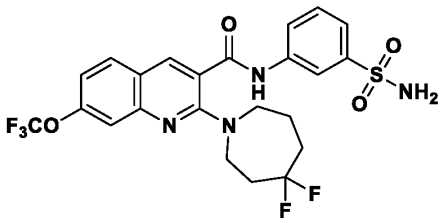
[00593] To a solution of 6-(4,4-difluoroazepan-1-yl)-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-5-carboxylic acid (0.25 g, 0.8 mmol) in dichloromethane (8 mL) was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.37 g, 0.97 mmol) and 4-dimethylaminopyridine (DMAP) (0.05 g, 0.41 mmol) at 0 °C and the mixture was stirred at room temperature for 12 hours. After completion of reaction, solvent was removed under reduced pressure. The residue was

dissolved into acetonitrile (8 mL) and 3-aminobenzenesulfonamide (0.17 g, 0.97 mmol) was added and refluxed for 12 hours. After completion of the reaction, acetonitrile was removed in vacuo and diluted with water then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The crude material was purified by reversed phase prep-HPLC to afford 6-(4,4-difluoroazepan-1-yl)-1-methyl-*N*-(3-sulfamoylphenyl)-1H-pyrrolo[2,3-*b*]pyridine-5-carboxamide as a white solid. LRMS (ESI): Calcd $[M+H]^+$: 464.16, found: 464.25.

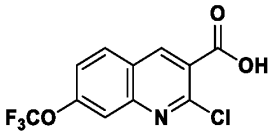
[00594] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.36 (s, 1H), 7.99 (s, 1H), 7.83-7.80 (m, 1H), 7.52 (d, J = 4.8 Hz, 2H), 7.37 (s, 2H), 7.25 (d, J = 3.2 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H), 3.72 (s, 3H), 3.65-3.63 (m, 2H), 3.48 (t, J = 6.0 Hz, 2H), 2.42-2.38 (m, 2H), 2.04-1.99 (m, 2H), 1.86-1.85 (m, 2H).

Compound 61

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7-(trifluoromethoxy)quinoline-3-carboxamide



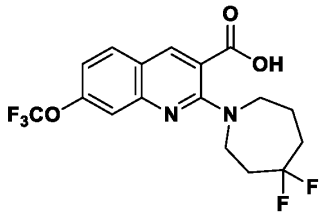
Synthesis of 2-chloro-7-(trifluoromethoxy)quinoline-3-carboxylic acid



[00595] To a stirred solution of 2-chloro-7-(trifluoromethoxy)quinoline-3-carbaldehyde (2.0 g, 7.2 mmol) in ethanol (20 mL) was added silver nitrate (1.95 g, 11.5 mmol) and a solution of sodium hydroxide (1.44 g, 36.0 mmol) in water (10 mL) at room temperature and stirred for 5 hours. After completion of reaction, the mixture was filtered through celite pad and the solvent was removed under reduced pressure. The crude material was diluted with water followed by acidification with 1*N* hydrochloric acid solution then extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude material which was

triturated with diethyl ether and n-pentane to give 2-chloro-7-(trifluoromethoxy)quinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethoxy)quinoline-3-carboxylic acid



[00596] To a solution of 2-chloro-7-(trifluoromethoxy)quinoline-3-carboxylic acid (1.0 g, 3.4 mmol) in *N*, *N*-dimethylformamide (10 mL) was added 4,4-difluoroazepane hydrogen chloride (0.87 g, 5.1 mmol) and potassium carbonate (2.3 g, 17 mmol). The mixture was heated at 80 °C for 12 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water followed by acidification with 1*N* hydrochloric acid solution then extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford the crude material which was purified through trituration with diethyl ether and n-pentane to afford 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethoxy)quinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-7-(trifluoromethoxy)quinoline-3-carboxamide

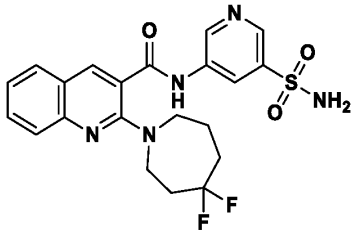
[00597] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-(trifluoromethoxy)quinoline-3-carboxylic acid (0.25 g, 0.64 mmol) in dichloromethane (2.5 mL) was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (0.36 g, 1.0 mmol) and 4-dimethylaminopyridine (DMAP) (0.04 g, 0.32 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, dichloromethane was evaporated under reduced pressure to obtain the crude mass which was dissolved in acetonitrile (3.0 mL) and to this, a solution of 3-aminobenzenesulfonamide (0.12 g, 0.77 mmol) was added and the resultant reaction mixture was refluxed for 12 hours. After completion of reaction, acetonitrile was removed under rotatory evaporation. The crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated. The crude material was purified by reverse-

phase HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-7-(trifluoromethoxy)quinoline-3-carboxamide as a pale yellow solid. LRMS (ESI): Calcd $[M+H]^+$: 545.13, found: 544.95.

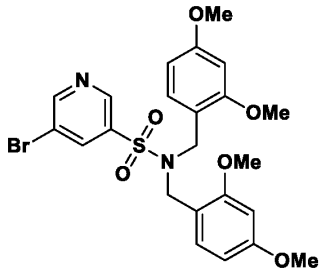
[00598] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.44 (s, 1H), 8.30 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.86-7.85 (m, 1H), 7.58-7.53 (m, 2H), 7.48 (s, 1H), 7.41 (s, 2H), 7.28 (d, J = 8.4 Hz, 1H), 3.77-3.76 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.45-2.37 (m, 2H), 2.01-1.96 (m, 2H), 1.90-1.89 (m, 2H).

Compound 62

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(5-sulfamoylpyridin-3-yl) quinoline-3-carboxamide

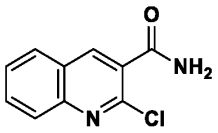


Synthesis of 5-bromo-N,N-bis(2,4-dimethoxybenzyl) pyridine-3-sulfonamide



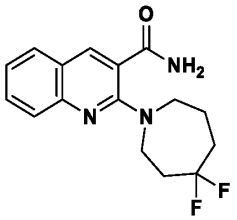
[00599] To a solution of 5-bromo-*N, N*-bis(2,4-dimethoxybenzyl) pyridine-3-sulfonamide (0.50 g, 1.95 mmol) in dichloromethane (5 mL) was added bis(2,4-dimethoxybenzyl) amine (0.74 g, 2.3 mmol) and *N ,N*,-diisopropylethylamine (1.0 mL, 5.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude mass was diluted with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford 5-bromo-*N, N*-bis(2,4-dimethoxybenzyl) pyridine-3-sulfonamide as an off-white solid.

Synthesis of 2-chloroquinoline-3-carboxamide



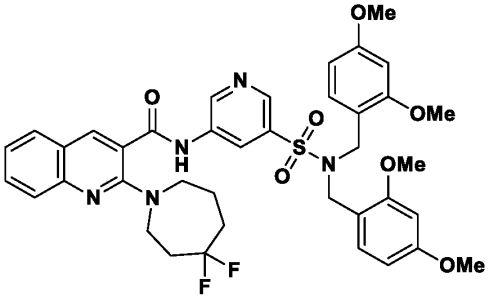
[00600] To a solution of 2-chloroquinoline-3-carboxylic acid (4.0 g, 19.32 mmol) in dichloromethane (40 mL) was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium3-oxide hexafluorophosphate (HATU) (11.0 g, 28.98 mmol) and ammonium carbonate (18.5 g, 193.2 mmol) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-chloroquinoline-3-carboxamide as an off-white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide



[00601] To a solution of 2-chloroquinoline-3-carboxamide (1.5 g, 1.25 mmol) in *N,N*-dimethylformamide (15 mL) was added 4,4-difluoroazepane hydrogen chloride (1.5 g, 8.7 mmol) and potassium carbonate (3 g, 2.2 mmol). The reaction mixture was heated at 80 °C for 12 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate then concentrated. The crude material was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide as a yellow liquid.

Synthesis of N-(5-(N, N-bis(2,4-dimethoxybenzyl)sulfamoyl) pyridin-3-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00602] To a solution of 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.25 g, 0.82 mmol) and 5-bromo-*N, N*-bis(2,4-dimethoxybenzyl) pyridine-3-sulfonamide (0.59 g, 0.98 mmol) in 1,4-dioxane (2.5 mL) was cesium carbonate (0.8 g, 2.46 mmol) at room temperature. The reaction mixture was degassed with nitrogen for 20 min, then BrettPhos Pd G3 (0.074 g, 0.08 mmol) was added and heated at 100 °C for 24 hours under nitrogen atmosphere. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate then concentrated under reduced pressure. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(5-(*N, N*-bis(2,4-dimethoxybenzyl) sulfamoyl) pyridin-3-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

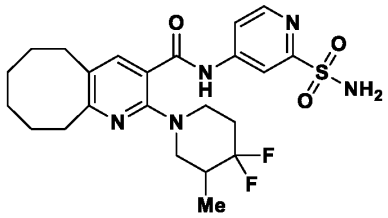
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(5-sulfamoylpyridin-3-yl) quinoline-3-carboxamide

[00603] To a stirred solution of *N*-(5-(*N,N*-bis(2,4-dimethoxybenzyl) sulfamoyl) pyridin-3-yl)-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.15 g, 0.20 mmol) in dichloromethane (2.5 mL), was added trifluoroacetic acid (TFA) (2.5 mL) at 0 °C and the reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the excess of trifluoroacetic acid was removed in vacuo. The residue obtained was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layers were separated, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material which was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to give 2-(4,4-difluoroazepan-1-yl)-*N*-(5-sulfamoylpyridin-3-yl)quinoline-3-carboxamide as an off-white solid. LRMS (ESI): Calcd $[M+H]^+$: 462.14, found: 461.15.

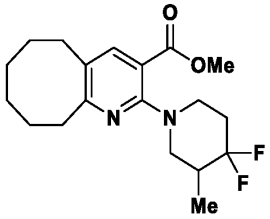
[00604] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H), 8.98 (d, J = 2.4 Hz, 1H), 8.73-8.70 (m, 2H), 8.40 (brs, 1H), 7.84 (d, J = 8 Hz, 1H), 7.70 (brs, 2H), 7.65 (t, J = 7.6 Hz, 2H), 7.33-7.29 (m, 1H), 3.76 (t, J = 2.4 Hz, 2H), 3.59 (t, J = 6 Hz, 2H), 2.39-2.37 (m, 2H), 2.01-1.99 (m, 2H), 1.96-1.89 (m, 2H).

Compound 63

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide

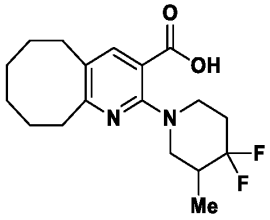


Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylate



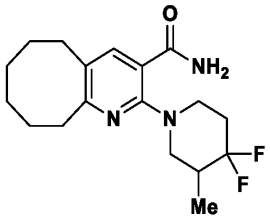
[00605] To a solution of methyl 2-chloro-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylate (0.30 g, 1.2 mmol) in *N*,*N*-dimethylformamide (1.5 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.25 g, 1.4 mmol) and potassium carbonate (0.66 g, 4.8 mmol) and the mixture was heated at 100 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The crude material was triturated with diethyl ether and n-pentane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxylic acid



[00606] To a solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylate (0.15 g, 0.42 mmol) in a mixture of tetrahydrofuran (5 mL) and methanol (5 mL) was added lithium hydroxide (0.04 g, 1.68 mmol) and water (5 mL) at ambient temperature and stirred for 12 hours at room temperature. After completion of reaction, the solvent was evaporated under vacuum and the crude residue was diluted with water and acidified with 1*N* hydrochloric acid then extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by washing with diethyl ether and n-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylic acid as a white solid.

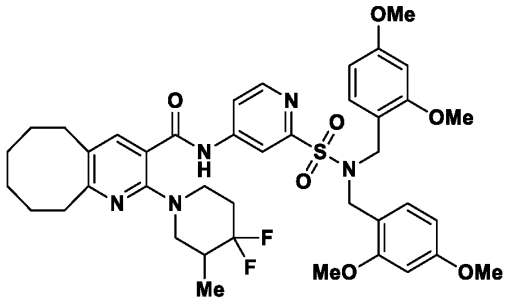
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide



[00607] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylic acid (0.13 g, 0.39 mmol) in *N*,*N*-dimethylformamide (1.3 mL) was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (0.22 g, 0.58 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (0.35 mL, 1.95 mmol) and ammonium chloride (0.20 g, 3.9 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, the crude material was diluted with

ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified through trituration with diethyl ether and n-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide



[00608] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxamide (0.09 g, 0.27 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.23 g, 0.44 mmol), cesium carbonate (0.17 g, 0.54 mmol) and BrettPhos Pd G3 (0.02 g, 0.02 mmol) under nitrogen atmosphere and heated the mixture at 100 °C for 48 hours. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, and the compound was diluted with water then extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carboxamide

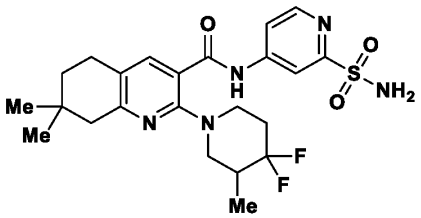
[00609] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxamide (**7**, 0.09 g, 0.12 mmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (0.50 mL) at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion, solvent was evaporated and the residue

thus obtained was dissolved in ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum to afford the crude material. The crude material was purified by flash column chromatography with a gradient of 30-35% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxamide as a white solid. MS (ESI): Calcd $[M+H]^+$: 494.20, found: 494.20.

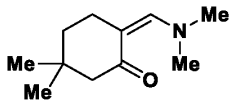
[00610] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 7.83-7.81 (m, 1H), 7.63 (s, 1H), 7.45 (s, 2H), 3.73-3.55 (m, 2H), 3.06 (t, J = 10.8 Hz, 1H), 2.86-2.80 (m, 2H), 2.73-2.71 (m, 2H), 2.14-2.05 (m, 2H), 1.98-1.89 (m, 1H), 1.86-1.63 (m, 4H), 1.34-1.20 (m, 5H), 0.89 (d, J = 6.8 Hz, 3H).

Compound 64

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

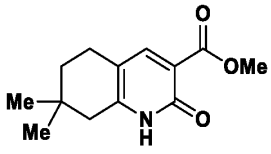


Synthesis of (Z)-2-((dimethylamino)methylene)-5,5-dimethylcyclohexan-1-one



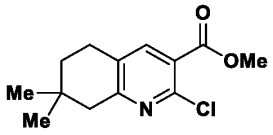
[00611] A mixture of 3,3-dimethylcyclohexan-1-one (2.0 g, 16 mmol) and 1-tert-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (3.0 g, 17.6 mmol) was heated at 80 °C for 12 hours. After completion of reaction, the solvent was removed under rotatory to obtain the crude (*Z*)-2-((dimethylamino)methylene)-5,5-dimethylcyclohexan-1-one as a brown liquid which was subjected into next step without any analysis.

Synthesis of methyl 2-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



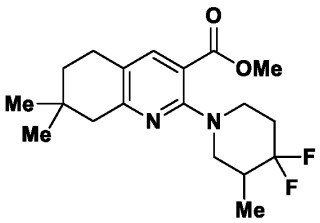
[00612] To a solution of crude *(Z)-2-((dimethylamino)methylene)-5,5-dimethylcyclohexan-1-one* (2.3 g, 13 mmol) in methanol (30 mL) was added sodium methoxide (2.1 g, 39 mmol) and methyl 3-amino-3-oxopropanoate (4.6 g, 39 mmol) at room temperature and slowly heated to 80 °C under nitrogen atmosphere for 12 hours. After completion of reaction, the solvent was evaporated and resulting crude materials was purified by trituration with acetonitrile and n-pentane to afford methyl 2-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-chloro-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00613] A mixture of methyl 2-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.62 g, 2.6 mmol) and phosphorus oxychloride ($POCl_3$) (6 mL) was heated to 110 °C for 12 hours. After the completion of reaction, the reaction mixture was then cooled to room temperature and excess of $POCl_3$ was distilled out. The crude residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuum to afford the crude materials which was triturated with diethyl ether and n-pentane to afford methyl 2-chloro-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

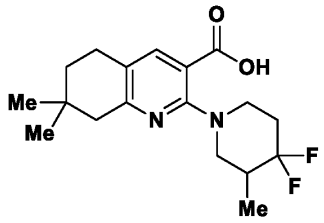
Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00614] To a solution of methyl 2-chloro-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.30 g, 1.2 mmol) in *N*, *N*-dimethylformamide (1.5 mL) was added 4,4-difluoro-3-methylpiperidine hydrogen chloride (0.25 g, 1.4 mmol) and potassium carbonate (0.66 g, 4.8 mmol). The mixture was heated at 100 °C for 48 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction

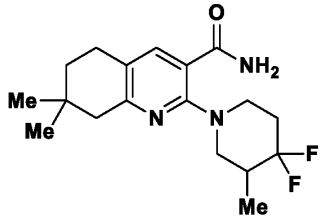
mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was triturated with diethyl ether and n-pentane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a yellow liquid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00615] To a solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.2 g, 0.56 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) was added a solution of lithium hydroxide (0.05 g, 2.2 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the solvent was evaporated & diluted with water, acidified with 1*N* hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by trituration with diethyl ether and n-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

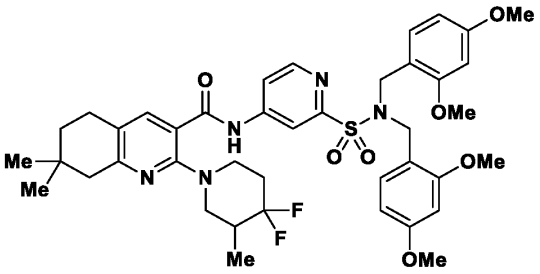
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00616] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.17 g, 0.50 mmol) in *N*, *N*-dimethylformamide (1.7 mL) was added (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-

oxide hexafluorophosphate (HATU) (0.29 g, 0.75 mmol), *N,N*-diisopropylethylamine (0.5 mL, 2.5 mmol) and ammonium chloride (0.27 g, 5 mmol) at 0 °C and stirred the mixture at room temperature for 12 hours. The progress of the reaction was monitor by TLC. After completion of reaction, the crude material was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was triturated with diethyl ether and n-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00617] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.11 g, 0.32 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.20 g, 0.38 mmol), cesium carbonate (0.20 g, 0.64 mmol) and BrettPhos Pd G3 (0.02 g, 0.032 mmol) under nitrogen atmosphere and heated the reaction mixture at 100 °C for 48 hours. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was evaporated, and the crude mass was diluted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

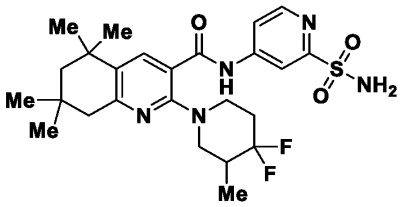
[00618] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-

carboxamide (0.12 g, 0.15 mmol) in dichloromethane (1.2 mL) was added trifluoroacetic acid (0.6 mL) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and the crude residue was dissolved into ethyl acetate, washed with sodium bicarbonate solution. The followed by brine solution, dried over anhydrous sodium sulfate and concentrated in vacuum to obtain the crude material which was purified by flash column chromatography with a gradient of 30-35% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7,7-dimethyl-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid. LRMS (ESI): Calcd $[M+H]^+$: 494.20, found: 494.15.

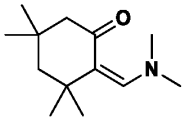
[00619] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.36 (s, 1H), 7.78 (d, J = Hz, 1H), 7.62 (s, 1H), 7.45 (s, 2H), 3.58 (t, J = 16 Hz, 2H), 3.05 (t, J = 11.6 Hz, 1H), 2.81 (t, J = 11.6 Hz, 1H), 2.78-2.71 (m, 2H), 2.53-2.50 (m, 2H), 2.11-2.06 (m, 2H), 1.91-1.84 (m, 1H), 1.55-1.53 (m, 2H), 0.97 (s, 6H), 0.089 (d, J = 6.8 Hz, 3H).

Compound 65

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

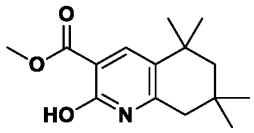


Synthesis of (Z)-2-((dimethylamino)methylene)-3,3,5,5-tetramethylcyclohexan-1-one



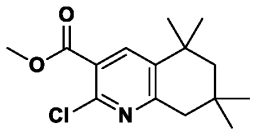
[00620] To a stirred solution of 3,3,5,5-tetramethylcyclohexan-1-one (15 g, 97 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (20 g, 107 mmol) was added at room temperature. The reaction mixture was heated at 120 °C for 12 hours. After reaction completion, the reaction mixture was concentrated to afford the crude (*Z*)-2-((dimethylamino)methylene)-3,3,5,5-tetramethylcyclohexan-1-one as a brown liquid, which was used in the next step without further purification.

Synthesis of methyl 2-hydroxy-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



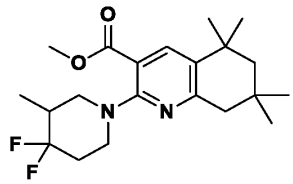
[00621] To a stirred solution of (*Z*)-2-((dimethylamino)methylene)-3,3,5,5-tetramethylcyclohexan-1-one (20 g, 96 mmol) in methanol (50 mL) was added methyl 2-cyanoacetate (11 g, 114 mmol) dropwise and the reaction mixture was heated at 80 °C for 18 hours. After reaction completion, the reaction mixture was concentrated and the residue was purified by flash chromatography with a gradient of 70-80% ethyl acetate in hexane to afford methyl 2-hydroxy-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a gummy brown liquid.

Synthesis of methyl 2-chloro-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00622] A mixture of phosphorus oxychloride (3 mL) and methyl 2-hydroxy-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.3 g, 1.1 mmol) was heated at 110 °C for 18 hours. After reaction completion, excess phosphorus oxychloride distilled out. The residue was poured into ice-cold water, neutralized with saturated solution of sodium bicarbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30 % ethyl acetate in hexane to afford methyl 2-chloro-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

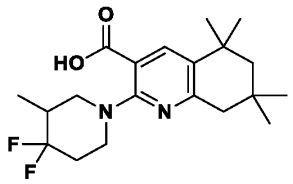
Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00623] To a stirred solution of methyl 2-chloro-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.25 g, 0.8 mmol) in *N,N*-dimethylformamide (3 mL), was

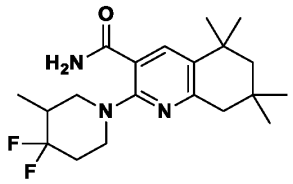
added 4,4-difluoro-3-methylpiperidine hydrochloride (0.22 g, 1.3 mmol) and potassium carbonate (0.55 g, 4.0 mmol) at room temperature. The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00624] To a stirred solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.2 g, 0.52 mmol) in methanol (1.0 mL) and tetrahydrofuran (1.0 mL), an aqueous solution of lithium hydroxide (0.072 g, 3 mmol) was added and the mixture was stirred for 12 hours at room temperature. After reaction completion, the solvent was removed in vacuo. The residue was diluted with water, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as an off white solid.

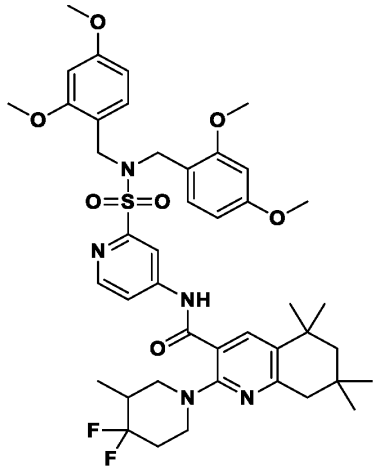
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00625] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.15 g, 0.4 mmol) in *N,N*-dimethylformamide

(5 mL) was added HATU (0.23 g, 0.61 mmol), *N*,*N*-diisopropylethylamine (0.5 mL, 3.05 mmol) and ammonium chloride (0.21 g, 4.1 mmol) at 0 °C. The mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis ofN-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00626] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.14 g, 0.38 mmol) in 1,4-dioxane (3 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.25 g, 0.46 mmol), cesium carbonate (0.25 g, 0.76 mmol) and BrettPhos Pd G3 (0.03 g, 0.04 mmol) under nitrogen atmosphere and the mixture was heated at 100 °C for 24 hours. After reaction completion, the solvent was removed in vacuo and the residue was diluted with water and ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The crude mixture was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off white solid.

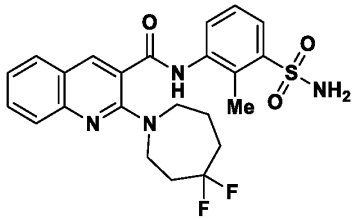
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00627] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.1 g, 0.12 mmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, solvent was removed in vacuo and the residue was dissolved into ethyl acetate and washed with a saturated solution of sodium bicarbonate. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-35% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5,7,7-tetramethyl-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. Yield: 0.01 g, 15%; LRMS (ESI): Calcd $[M+H]^+$: 522.23, found: 522.30.

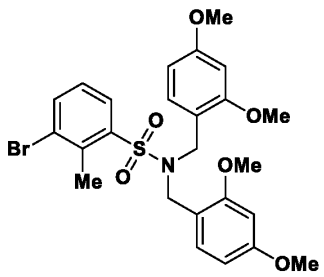
[00628] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.60 (d, J = 1.4 Hz, 1H), 8.38 (s, 1H), 7.82-7.80 (m, 2H), 7.44 (s, 2H), 3.61 (t, J = 15.6 Hz, 2H), 3.05 (t, J = 11.2 Hz, 1H), 2.82 (t, J = 12.4 Hz, 1H), 2.57 (s, 2H), 2.12-2.04 (m, 2H), 1.94-1.75 (m, 1H), 1.58 (s, 2H), 1.27 (s, 6H), 0.98 (s, 6H), 0.89 (d, J = 6.8 Hz, 3H).

Compound 66

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(2-methyl-3-sulfamoylphenyl) quinoline-3-carboxamide

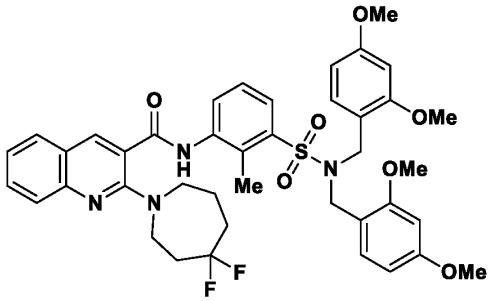


Synthesis of 3-bromo-N,N-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide



[00629] To a solution of 3-bromo-2-methylbenzenesulfonyl chloride (0.5 g, 1.9 mmol) in dichloromethane (5 mL) was added bis(2,4-dimethoxybenzyl) amine (0.71 g, 2.25 mmol) and *N,N*-diisopropylethylamine (1 mL, 5.62 mmol) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude mass was diluted with water and extracted with dichloromethane. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford 3-bromo-*N,N*-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide as an off-white solid.

Synthesis of N-(3-(N,N-bis(2,4-dimethoxybenzyl) sulfamoyl)-2-methylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00630] To a solution of 3-bromo-*N,N*-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide (0.54 g, 0.98 mmol) and 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.25 g, 0.82 mmol) in 1,4-dioxane (2.5 mL) was added cesium carbonate (0.53 g, 1.64 mmol). The reaction mixture was degassed with nitrogen for 20 min, then BrettPhos Pd G3 (0.025 g, 0.08 mmol) was added. The reaction mixture was heated at 100 °C for 24 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude mass was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)-2-methylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(2-methyl-3-sulfamoylphenyl)quinoline-3-carboxamide

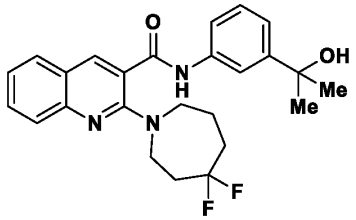
[00631] To a stirred solution of *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)-2-methylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.30 g, 0.39 mmol) in

dichloromethane (3 mL) was added trifluoroacetic acid (TFA) (3 mL) at 0 °C and stirred the reaction mixture at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the excess of trifluoroacetic acid was distilled. The residue obtained was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material which was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(2-methyl-3-sulfamoylphenyl)quinoline-3-carboxamide as an off white solid. LRMS (ESI): Calcd $[M+H]^+$: 475.16, found: 475.10.

[00632] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.39 (brs, 1H), 7.88 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 3.6 Hz, 2H), 7.50 (brs, 2H), 7.43 (t, J = 8.0 Hz, 1H), 7.33-7.29 (m, 1H), 3.76 (d, J = 7.6 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 2.58 (s, 3H), 2.49-2.39 (m, 2H), 2.05-2.39 (m, 2H), 2.0-1.94 (m, 2H).

Compound 67

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(2-hydroxypropan-2-yl)phenyl)quinoline-3-carboxamide



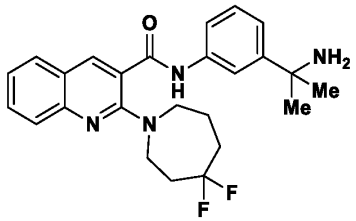
[00633] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.28 mg, 0.092 mmol) in 1,4-dioxane (3 mL) was added 2-(3-bromophenyl)propan-2-ol (0.02 mg, 0.092 mmol) and cesium carbonate (0.06 mg, 0.18 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.017 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by reserve-phase HPLC to afford 2-(4,4-difluoroazepan-1-yl)-N-(3-(2-hydroxypropan-2-yl)phenyl)quinoline-3-carboxamide as a white powder. Yield: 2.3 mg, 5.7%; LRMS (ESI): Calcd $[M+H]^+$: 440.21, found: 440.35.

[00634] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.49 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 6.5 Hz, 2H), 7.45 (t, *J* = z7.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 3.88

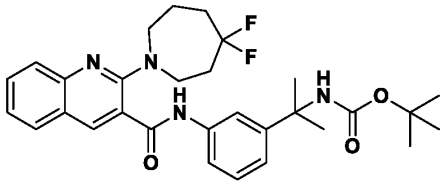
– 3.81 (m, 2H), 3.80 – 3.73 (m, 2H), 2.46 – 2.35 (m, 2H), 2.19 – 2.07 (m, 2H), 1.99 – 1.91 (m, 2H), 1.6 (s, 3H).

Compound 68

Synthesis of N-(3-(2-aminopropan-2-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of tert-butyl (2-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)propan-2-yl)carbamate



[00635] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (15 mg, 0.05 mmol) in 1,4-dioxane (3 mL) was added *tert*-butyl (2-(3-bromophenyl)propan-2-yl)carbamate (15.6 mg) and cesium carbonate (32 mg, 0.1 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (4.5 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by reserve-phase HPLC to afford *tert*-butyl (2-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)propan-2-yl)carbamate as a white powder.

Synthesis of N-(3-(2-aminopropan-2-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

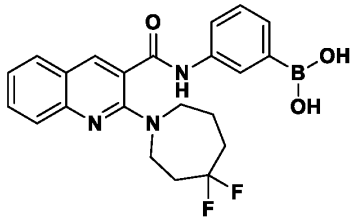
[00636] To a solution of *tert*-butyl (2-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)propan-2-yl)carbamate (8.6 mg, 0.016 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (25 µL) at ambient temperature. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate,

filtered, then concentrated. The residue was purified by reverse-phase HPLC to give N-(3-(2-aminopropan-2-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white powder. Yield: 4.4 mg, 63%; LRMS (ESI): Calcd $[M+H]^+$: 439.23, found: 439.30.

[00637] ^{1}H NMR (400 MHz, MeOD) δ 8.25 (s, 1H), 7.98 (t, J = 1.9 Hz, 1H), 7.75 – 7.64 (m, 2H), 7.63 – 7.55 (m, 1H), 7.52 – 7.48 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.31 – 7.20 (m, 2H), 3.79 – 3.72 (m, 2H), 3.64 (t, J = 6.0 Hz, 2H), 2.4 – 2 2.27 (m, 2H), 2.00 – 1.87 (m, 4H), 1.67 (s, 6H).

Compound 69

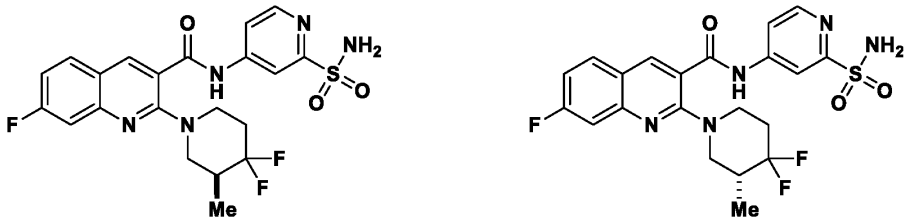
Synthesis of (3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)boronic acid



[00638] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (12.3 mg, 40.0 μmol) in DCM (1 mL) and DMF (1 mL) was added (3-aminophenyl)boronic acid (5.48 mg, 40.0 μmol), HATU (22.8 mg, 60.0 μmol), and DMAP (14.7 mg, 120 μmol) at room temperature. The reaction mixture was stirred at room temperature for 24 hrs. After reaction completion, the reaction mixture was diluted with MeCN (3 mL) and purified by reverse-phase HPLC to afford (3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)boronic acid (3.9 mg, 23 %) as a white powder; LRMS (ESI): Calcd $[M+H]^+$: 426.18, found: 426.25.

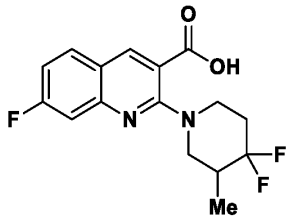
[00639] ^{1}H NMR (400 MHz, MeOD) δ 8.60 – 8.55 (m, 1H), 7.97 – 7.92 (m, 3H), 7.85 – 7.78 (m, 2H), 7.54 – 7.50 (m, 1H), 7.50 – 7.42 (m, 2H), 3.99 – 3.93 (m, 2H), 3.89 – 3.85 (m, 2H), 2.56 – 2.41 (m, 2H), 2.19 – 2.15 (m, 2H), 2.10 – 2.05 (m, 2H).

Compounds 70 and 71



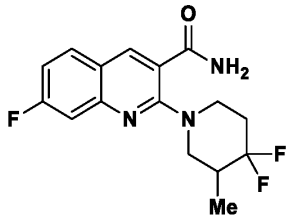
Synthesis of (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide and (R)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid



[00640] To a stirred solution of 2-chloro-7-fluoroquinoline-3-carboxylic acid (0.11 g, 0.5 mmol) in *N,N*-dimethylformamide (2 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.086 g, 0.5 mmol) and potassium carbonate (0.345 g, 2.5 mmol) at room temperature. The reaction mixture was heated at 60 °C for 72 hours. After completion of reaction, the reaction mixture was diluted with water and acidified with 1N HCl then extracted with ethyl acetate. The organic layers were washed with brine and dried with anhydrous sodium sulfate, then filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography with a gradient of 0-20% methanol in dichloromethane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid as an orange solid.

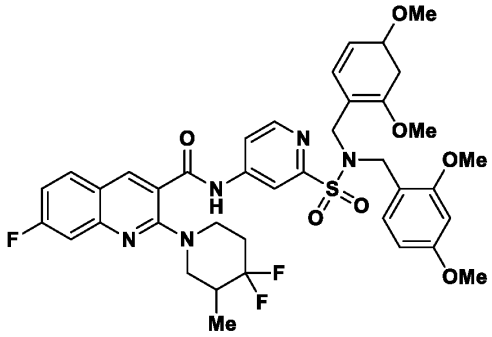
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide



[00641] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.065 g, 0.2 mmol) in dichloromethane (2 mL) in dichloromethane (2 mL) was added [(dimethylamino)({3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium hexafluoro-λ^5-phosphanuide (HATU) (0.11 g, 0.3 mmol) and ammonium carbonate (0.096 g, 1 mmol) was added at room temperature. The resulting mixture was slowly warmed to room temperature and stirred for 24 hours. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and

concentrated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 0-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide as a light yellow oil.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-(N-(2,4-dimethoxybenzyl)-N-((2,4-dimethoxycyclohexa-1,5-dien-1-yl)methyl)sulfamoyl)pyridin-4-yl)-7-fluoroquinoline-3-carboxamide



[00642] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (0.021 g, 0.064 mmol) in 1,4-dioxane (2 mL) was added cesium carbonate (0.042 g, 0.99 mmol), BrettPhos Pd G3 (0.0012 g, 0.013 mmol) and 4-bromo-*N*,*N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.034 g, 0.064 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was slowly warmed to room temperature and then heated at 100 °C for 24 hours. After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash column chromatography with a gradient of ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-(N-(2,4-dimethoxybenzyl)-N-((2,4-dimethoxycyclohexa-1,5-dien-1-yl)methyl)sulfamoyl)pyridin-4-yl)-7-fluoroquinoline-3-carboxamide as a yellow solid.

Synthesis of (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide and (R)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00643] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-(N-(2,4-dimethoxybenzyl)-N-((2,4-dimethoxycyclohexa-1,5-dien-1-yl)methyl)sulfamoyl)pyridin-4-yl)-7-fluoroquinoline-3-carboxamide (0.040 g, 0.052 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.079 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was concentrated and the residue was purified by flash column chromatography with a gradient of ethyl acetate in

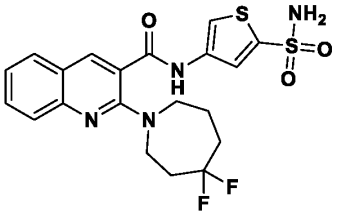
hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as an off-white solid. (R and S) 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide was purified by preparative SFC to give the title compounds, (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide and (R)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide.

[00644] Peak-1: ^{1}H NMR (400 MHz, CD_3CN) δ 8.61 (d, *J* = 5.5 Hz, 1H), 8.54 (s, 1H), 8.41 – 8.37 (m, 1H), 7.97 – 7.89 (m, 1H), 7.79 (dd, *J* = 5.5, 2.1 Hz, 1H), 7.47 (dd, *J* = 10.6, 2.3 Hz, 1H), 7.32 – 7.22 (m, 1H), 3.92 – 3.74 (m, 2H), 3.35 – 3.23 (m, 1H), 3.35 – 3.24 (m, 1H), 3.06 – 2.98 (m, 3H), 2.18 – 1.99 (m, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). LRMS (ESI): Calcd $[M+H]^+$: 480.13, found: 480.20.

[00645] Peak-2: ^{1}H NMR (400 MHz, CD_3CN) δ 8.61 (d, *J* = 5.5 Hz, 1H), 8.54 (s, 1H), 8.41 – 8.37 (m, 1H), 7.97 – 7.89 (m, 1H), 7.79 (dd, *J* = 5.5, 2.1 Hz, 1H), 7.47 (dd, *J* = 10.6, 2.3 Hz, 1H), 7.32 – 7.22 (m, 1H), 3.92 – 3.74 (m, 2H), 3.35 – 3.23 (m, 1H), 3.35 – 3.24 (m, 1H), 3.06 – 2.98 (m, 3H), 2.18 – 1.99 (m, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). LRMS (ESI): Calcd $[M+H]^+$: 480.13, found: 480.25.

Compound 72

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(5-sulfamoylthiophen-3-yl)quinoline-3-carboxamide



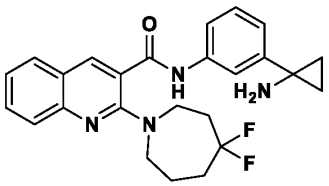
[00646] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (12.3 mg, 40 μmol) in DCM (1 mL) was added oxalyl chloride (6.3 μL, 72 μmol) at room temperature. A catalytic amount of DMF was added and the reaction mixture was stirred at room temperature for 15 mins. A solution of 5-aminothiophene-2-sulfonamide (7.1 mg, 40 μmol) and DIPEA (21 μL, 120 μmol) in DMF (1 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 96 hrs. The reaction mixture was concentrated and diluted with MeCN (4 mL) then purified using reverse-phase HPLC to afford 2-(4,4-difluoroazepan-1-yl)-

N-(5-sulfamoylthiophen-2-yl)quinoline-3-carboxamide (1.30 mg, 7 %) as a white powder; LRMS (ESI): Calcd $[M+H]^+$: 467.10, found: 467.15.

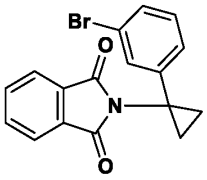
[00647] ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.32 (m, 1H), 7.98 – 7.89 (m, 1H), 7.78 – 7.74 (m, 1H), 7.72 – 7.68 (m, 1H), 7.65 – 7.59 (m, 2H), 7.35 – 7.30 (m, 1H), 3.78 – 3.72 (m, 2H), 3.58 – 3.52 (m, 2H), 2.46 – 2.34 (m, 2H), 2.12 – 2.01 (m, 2H), 1.95 – 1.88 (m, 2H).

Compound 73

Synthesis of N-(3-(1-aminocyclopropyl)phenyl)-2-(4,4-difluorocycloheptyl)quinoline-3-carboxamide

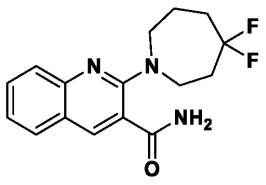


Synthesis of 2-(1-(3-bromophenyl)cyclopropyl)isoindoline-1,3-dione



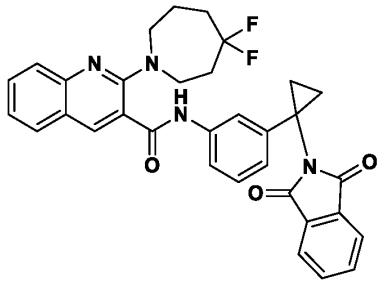
[00648] To a solution of phthalic anhydride (0.5 g, 3.4 mmol) in toluene (25 mL) was added 1-(3-bromophenyl)cyclopropan-1-amine (0.86 g, 4.1 mmol) and triethylamine (0.94 mL, 6.8 mmol). The reaction mixture was heated at 100 °C or 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and *n*-pentane to afford 2-[1-(3-bromophenyl)cyclopropyl]-1,3-isoindolinedione as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00649] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.9 g, 2.9 mmol) in *N*,*N*-dimethylformamide (16 mL) was added HATU (1 g, 4.4 mmol), *N*,*N*-diisopropylethylamine (2.56 mL, 14.7 mmol), and ammonium chloride (1.57 g, 29.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column using 70% ethyl acetate in hexane as an eluent to obtain 2-(4,4-difluorocycloheptyl)-3-quinolinecarboxamide as an off-white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(1-(1,3-dioxoisoindolin-2-yl)cyclopropyl)phenyl)quinoline-3-carboxamide



[00650] A solution of 2-(4,4-difluorocycloheptyl)-3-quinolinecarboxamide (0.5 g, 1.6 mmol) and 2-(1-(3-bromophenyl)cyclopropyl)isoindoline-1,3-dione (0.62 g, 1.86 mmol) in 1,4-dioxane (25 mL) was added cesium carbonate (1.1 g, 3.3 mmol). The reaction mixture was degassed with nitrogen followed then Xantphos (0.19 g, 0.33 mmol) and tris(dibenzylideneacetone)dipalladium (0.13 g, 0.16 mmol) were added. The reaction mixture was heated at 110 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 70% ethyl acetate in hexane to obtain 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(1-(1,3-dioxoisoindolin-2-yl)cyclopropyl)phenyl)quinoline-3-carboxamide as an off white solid.

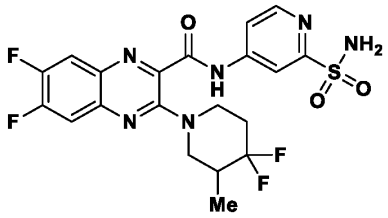
Synthesis of N-(3-(1-aminocyclopropyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00651] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(1-(1,3-dioxoisoindolin-2-yl)cyclopropyl)phenyl)quinoline-3-carboxamide (0.330 g, 0.58 mmol) in ethanol (19 mL) was added hydrazine hydrate (0.15 mL, 2.9 mmol) at 0 °C. The reaction mixture was warmed to room temperature then stirred for 2 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by Prep-HPLC to obtain *N*-(3-(1-aminocyclopropyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as an off-white solid. Yield: 0.082g, 32%; LRMS (ESI): Calcd $[M+H]^+$: 437.2, found: 437.4.

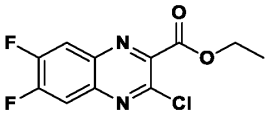
[00652] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.89-7.86 (m, 1H), 7.63-7.58 (m, 2H), 7.41 (br s, 2H), 3.82-3.79 (m, 2H), 3.67 (t, J = 6.0 Hz, 2H), 2.41-2.36 (m, 2H), 2.07-1.99 (m, 2H), 1.93-1.75 (m, 2H).

Compound 74

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide

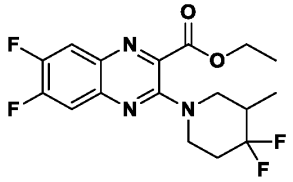


Synthesis of ethyl 3-chloro-6,7-difluoroquinoxaline-2-carboxylate



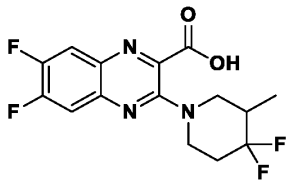
[00653] A round bottom flask was charged with a ethyl 6,7-difluoro-3-hydroxyquinoxaline-2-carboxylate (500 mg, 2 mmol) followed by phosphorous oxychloride (7 mL) at room temperature. The reaction mixture was stirred at 100 °C for 18 hours. After reaction completion, the reaction mixture was diluted with water, extracted with DCM, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford ethyl 3-chloro-6,7-difluoroquinoxaline-2-carboxylate as a white powder

Synthesis of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylate



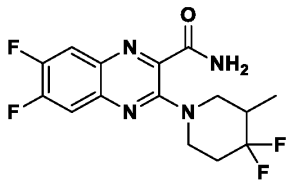
[00654] To a solution of ethyl 3-chloro-6,7-difluoroquinoxaline-2-carboxylate (100 mg, 0.41 mmol) in DMF (4.4 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (75 mg, 0.41 mmol) and potassium carbonate (305 mg, 2.04 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 72 hours. After reaction completion, the reaction mixture was diluted with chloroform and purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylate as a yellow oil.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylic acid



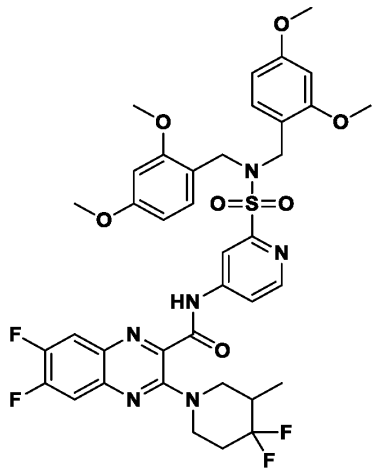
[00655] To a solution of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylate (126 mg, 034 mmol) in methanol (3.4 mL) and THF (12 mL) was added 1M NaOH solution (3.4 mL). The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was acidified with 1M HCl, extracted with DCM, dried with anhydrous sodium sulfate, filtered, then concentrated to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylic acid, which was used directly in the next step without further purification.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxamide



[00656] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxylic acid (116 mg, 0.34 mmol) in DCM (3.3 mL) was added oxalyl chloride (106 µL, 1.22 mmol) then a drop of DMF. The reaction mixture was stirred at room temperature for 15 mins. The reaction mixture was diluted with ethyl acetate (4 mL) then NH_4OH (2 mL) was added. The reaction mixture was stirred at room temperature for 72 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxamide as a yellow oil.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxamide



[00657] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxamide (0.16 g, 0.04 mmol) in 1,4-dioxane (3 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.028 g, 0.052 mmol) and cesium carbonate (0.03 g) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.006 g) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoroquinoxaline-2-carboxamide as an orange oil.

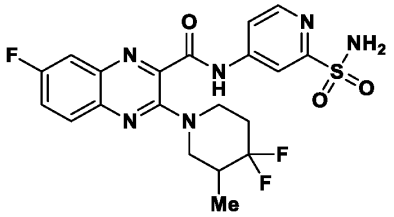
Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6,7-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide

[00658] To a solution of *tert-butyl (2-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)propan-2-yl)carbamate* (8.6 mg, 0.016 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (25 µL) at ambient temperature. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reverse-phase HPLC to give N-(3-(2-aminopropan-2-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow powder. Yield: 4.4 mg, 63%; LRMS (ESI): Calcd $[M+H]^+$: 499.12, found:499.27.

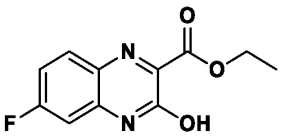
[00659] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.26 – 7.20 (m, 1 H), 7.11 – 7.08 (m, 1H), 6.96 – 6.90 (m, 1H), 6.68 (s, 1H), 4.40 – 4.30 (m, 1H), 4.0 – 3.88 (m, 1H), 3.48 – 3.27 (m, 1H), 3.00 – 2.92 (m, 1H), 2.79 (t, J = 5.9 Hz, 1H), 2.27 – 2.18 (m, 1H), 1.23 – 1.15 (m, 3H).

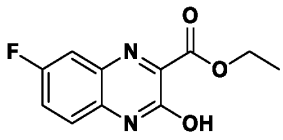
Compound 75

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide



Synthesis of ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylate and ethyl 7-fluoro-3-hydroxyquinoxaline-2-carboxylate

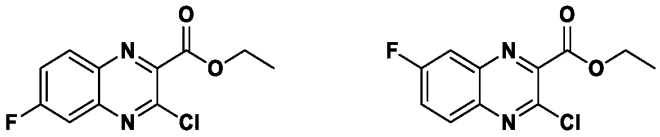




[00660] To a solution of 4-fluorobenzene-1,2-diamine (440 mg, 3.5 mmol) in ethanol (20 mL0 was added diethyl 2-oxomalonate (530 µL, 3.5 mmol) at room temperature. The reaction

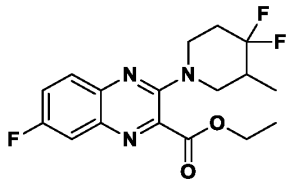
mixture was heated at 70 °C for 72 hours. After reaction completion, the reaction mixture was concentrated and the residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford a mixture of ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylate and ethyl 7-fluoro-3-hydroxyquinoxaline-2-carboxylate.

Synthesis of ethyl 3-chloro-6-fluoroquinoxaline-2-carboxylate and ethyl 3-chloro-7-fluoroquinoxaline-2-carboxylate



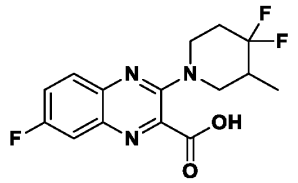
[00661] A round bottom flask was charged with a mixture of ethyl 6-fluoro-3-hydroxyquinoxaline-2-carboxylateethyl and 7-fluoro-3-hydroxyquinoxaline-2-carboxylate (260 mg) followed by phosphorous oxychloride (3.8 mL) at room temperature. The reaction mixture was stirred at 100 °C for 18 hours. After reaction completion, the reaction mixture was diluted with water, extracted with DCM, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford ethyl 3-chloro-6-fluoroquinoxaline-2-carboxylate and ethyl 3-chloro-7-fluoroquinoxaline-2-carboxylate as white powders.

Synthesis of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylate



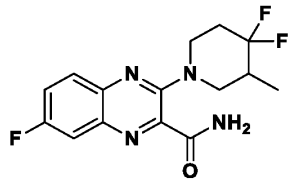
[00662] To a solution of ethyl 3-chloro-7-fluoroquinoxaline-2-carboxylate (110 mg, 0.48 mmol) in DMF (4.8 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (83 mg, 0.48 mmol) and potassium carbonate (335 mg, 2.4 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 72 hours. After reaction completion, the reaction mixture was diluted with chloroform and purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylate as a yellow oil.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylic acid



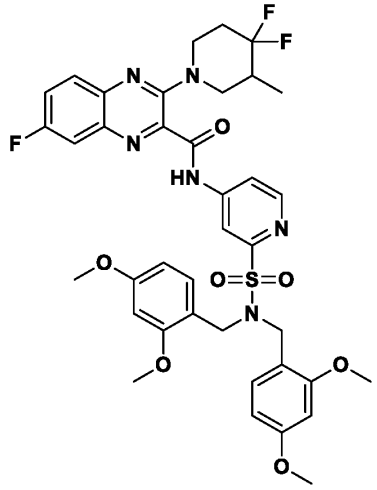
[00663] To a solution of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylate (153 mg, 0.43 mmol) in methanol (4.3 mL) and THF (16 mL) was added 1M NaOH solution (4.3 mL). The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was acidified with 1M HCl, extracted with DCM, dried with anhydrous sodium sulfate, filtered, then concentrated to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylic acid as a yellow oil, which was used directly in the next step without further purification.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide



[00664] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxylic acid (128 mg, 0.39 mmol) in DCM (4 mL) was added oxalyl chloride (124 µL, 1.4 mmol) then a drop of DMF. The reaction mixture was stirred at room temperature for 15 mins. The reaction mixture was diluted with ethyl acetate (4 mL) then NH4OH (2 mL) was added. The reaction mixture was stirred at room temperature for 72 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide as a yellow powder.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide



[00665] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide (0.35 mg, 0.11 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.064 mg, 0.11 mmol) and cesium carbonate (0.07 mg) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.020 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide as an orange oil.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

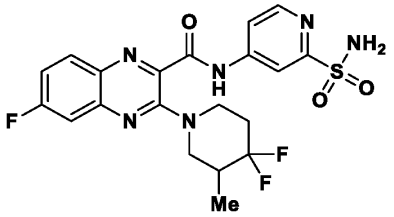
To a stirred solution of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide (74 mg, 0.095 mmol) in DCM (5 mL) was added TFA (147 µL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reverse-phase HPLC to give 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-

carboxamide as a yellow powder. Yield: 1.8 mg, 4%; LRMS (ESI): Calcd $[M+H]^+$: 481.13, found: 481.4.

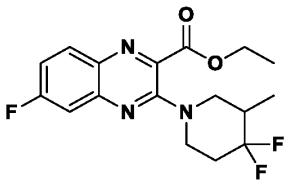
[00666] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 8.68 (d, J = 5.6 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 7.93-7.91 (m, 1H), 7.88-7.80 (m, 2H), 7.75-7.70 (m, 1H), 7.50 (s, 2H), 3.98-3.87 (m, 2H), 3.34-3.33 (m, 1H), 3.10 (t, J = 10.4 Hz, 1H), 2.24-2.21 (m, 2H), 2.01-1.95 (m, 1H), 0.95 (d J = 6.8 Hz, 3H).

Compound 76

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide

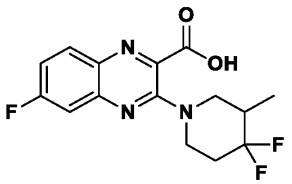


Synthesis of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylate



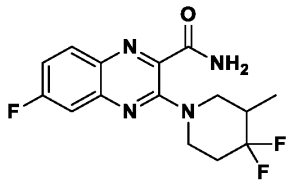
[00667] To a solution of ethyl 3-chloro-6-fluoroquinoxaline-2-carboxylate (54 mg, 0.24 mmol) in DMF (2.4 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (41 mg, 0.24 mmol) and potassium carbonate (166 mg, 1.2 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 72 hours. After reaction completion, the reaction mixture was diluted with chloroform and purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylate as a yellow oil.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylic acid



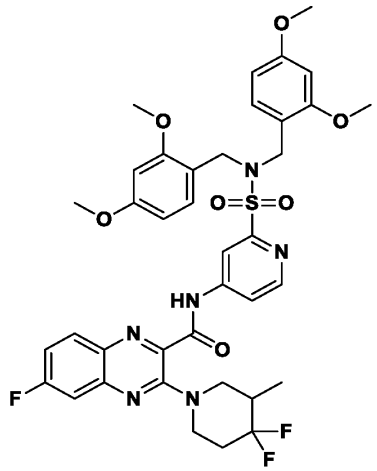
[00668] To a solution of ethyl 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylate (72 mg, 0.2 mmol) in methanol (2 mL) and THF (8 mL) was added 1M NaOH solution (2 mL). The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was acidified with 1M HCl, extracted with DCM, dried with anhydrous sodium sulfate, filtered, then concentrated to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylic acid as a yellow oil, which was used directly in the next step without further purification.

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide



[00669] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxylic acid (63 mg, 0.19 mmol) in DCM (2 mL) was added oxalyl chloride (61 μL, 0.9 mmol) then a drop of DMF. The reaction mixture was stirred at room temperature for 15 mins. The reaction mixture was diluted with ethyl acetate (4 mL) then NH_4OH (2 mL) was added. The reaction mixture was stirred at room temperature for 72 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide as a yellow powder.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide



[00670] To a solution of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide (0.37 mg, 0.114 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.067 mg, 0.114 mmol) and cesium carbonate (0.074 mg, 0.23 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.021 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide as an orange foam.

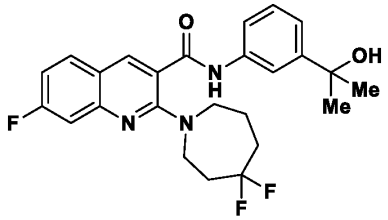
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

To a stirred solution of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide (64 mg, 0.082 mmol) in DCM (5 mL) was added TFA (126 µL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reverse-phase HPLC to give 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a yellow powder; Yield: 1.5 mg, 3.8%; LRMS (ESI): Calcd $[M+H]^+$: 481.13, found: 481.4

[00671] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.67 (d, J = 5.6 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.08-8.05 (m, 1H), 7.95-7.93 (m, 1H), 7.56-7.48 (m, 4H), 4.03-3.92 (m, 2H), 3.36-3.31 (m, 1H), 3.16-3.10 (m, 1H), 2.32-2.19 (m, 2H), 2.04-1.96 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H).

Compound 77

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-(2-hydroxypropan-2-yl)phenyl)quinoline-3-carboxamide

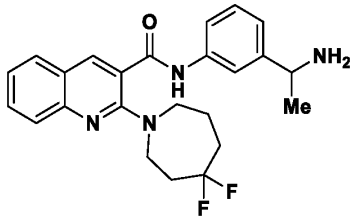


[00672] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.19 mg, 0.06 mmol) in 1,4-dioxane (5 mL) was added 2-(3-bromophenyl)propan-2-ol (0.013 mg, 0.06 mmol) and cesium carbonate (0.04 mg, 0.12 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.011 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by reserve-phase HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-(2-hydroxypropan-2-yl)phenyl)quinoline-3-carboxamide. Yield: 2mg, 7.3%; LRMS (ESI): Calcd $[M+H]^+$: 458.20, found:458.35.

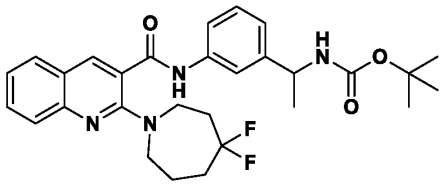
[00673] ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.90 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.80 (s, 1H), 7.64 – 7.59 (m, 1H), 7.48 (d, *J* = 10.5 Hz, 1H), 7.39 – 7.28 (m, 1H), 7.22 (td, *J* = 8.7, 2.3 Hz, 1H), 3.90 (dd, *J* = 6.9, 3.6 Hz, 2H), 3.79 (t, *J* = 5.7 Hz, 2H), 2.45 (d, *J* = 4.6 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.07 – 2.00 (m, 2H).

Compound 78

Synthesis of N-(3-(1-aminoethyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of tert-butyl (1-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)ethyl)carbamate



[00674] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (15 mg, 0.05 mmol) in 1,4-dioxane (3 mL) was added *tert*-butyl (1-(3-bromophenyl)ethyl)carbamate (15 mg) and cesium carbonate (32 mg, 0.1 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (4.5 mg) was added under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by reserve-phase HPLC to afford *tert*-butyl (1-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)ethyl)carbamate as a white powder.

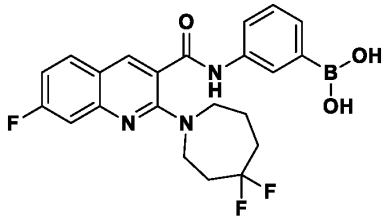
Synthesis of N-(3-(1-aminoethyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00675] To a solution of *tert*-butyl (1-(3-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)phenyl)ethyl)carbamate (12 mg, 0.023 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (35 μL) at ambient temperature. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reverse-phase HPLC to give *N*-(3-(1-aminoethyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamideas a white powder. Yield: 3.2 mg, 32%; LRMS (ESI): Calcd $[M+H]^+$: 425.21, found:425.35.

[00676] ^{1}H NMR (400 MHz, MeOD) δ 8.38 (s, 1H), 8.05 (t, *J* = 2.0 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.29 (m, 1H), 4.51 (q, *J* = 6.7 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.76 (t, *J* = 5.9 Hz, 2H), 2.48 – 2.42 (m, 3H), 2.14 – 2.07 (m, 2H), 2.05 – 1.99 (m, 2H), 1.69 (d, *J* = 6.7 Hz, 3H).

Compound 80

Synthesis of (3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)phenyl)boronic acid

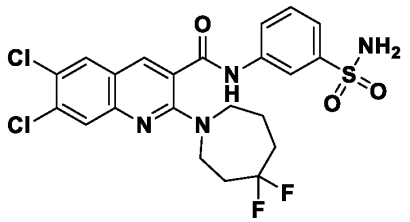


[00677] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (13 mg, 40 μmol) in DCM (1 mL) and DMF (1 mL) was added (3-aminophenyl)boronic acid (5.5 mg, 40 μmol), HATU (23 mg, 60 μmol), and DMAP (14.7 mg, 120 μmol) at room temperature. The reaction mixture was stirred at room temperature for 24 hrs. After reaction completion, the reaction mixture was diluted with MeCN (3 mL) and purified by reverse-phase HPLC to afford (3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)phenyl)boronic acid (2 mg, 9 %) as a white powder; LRMS (ESI): Calcd $[M+H]^+$: 444.17, found: 444.25.

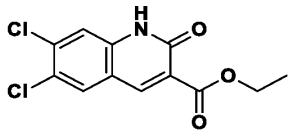
[00678] ^{1}H NMR (400 MHz, MeOD) δ 8.45 (s, 1H), 7.97 – 7.88 (m, 1H), 7.80 (dt, J = 7.7, 2.0 Hz, 1H), 7.54 – 7.37 (m, 3H), 7.28 – 7.20 (m, 1H), 3.96 – 3.88 (m, 2H), 3.85 – 3.77 (m, 2H), 2.53 – 2.40 (m, 2H), 2.18 – 2.03 (m, 4H).

Compound 82

Synthesis of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

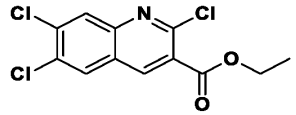


Synthesis of ethyl 6,7-dichloro-2-oxo-1,2-dihydroquinoline-3-carboxylate



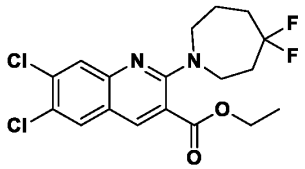
[00679] To a solution of 2-amino-4,5-dichlorobenzaldehyde (0.5 g, 2.6 mmol) in ethanol (10 mL) was added diethyl malonate (4.2 g, 26 mmol), piperidine (0.88 g, 10.4 mmol) and the mixture was heated at 80 °C for 5 hours. After reaction completion, the solvent was removed in vacuo. The crude mixture was washed with brine and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash chromatography with a gradient of 70-80% ethyl acetate in hexane to afford ethyl 6,7-dichloro-2-oxo-1,2-dihydroquinoline-3-carboxylate as a yellow solid.

Synthesis of ethyl 2,6,7-trichloroquinoline-3-carboxylate



[00680] A solution of phosphoryl chloride (4.5 mL) and ethyl 6,7-dichloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (0.45 g, 1.6 mmol) was heated at 110 °C for 12 hours. After reaction completion, excess phosphoryl chloride was distilled out and the residue was poured over with crushed ice, neutralized with saturated solution of sodium bicarbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford ethyl 2,6,7-trichloroquinoline-3-carboxylate as a yellow solid.

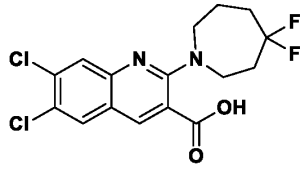
Synthesis of ethyl 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate



[00681] To a stirred solution of ethyl 2,6,7-trichloroquinoline-3-carboxylate (0.4 g, 1.3 mmol) in *N,N*-dimethylformamide (3 mL), 4,4-difluoroazepane hydrochloride (0.33 g, 1.9 mmol) and potassium carbonate (0.71 g, 5.2 mmol) were added at room temperature. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated under vacuum. The residue was purified by flash column chromatography with a

gradient of 30-40% ethyl acetate in hexane to afford ethyl 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate as a yellow solid.

Synthesis of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid



[00682] To a stirred solution of ethyl 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate (0.3 g, 0.74 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL), aqueous solution of lithium hydroxide (0.12 g, 3 mmol) in water (1 mL) was added. The mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was diluted with water, acidified with hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid as a brown solid.

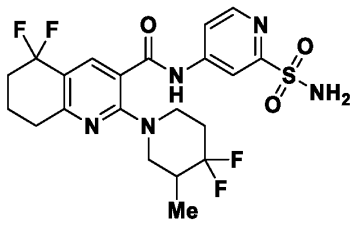
Synthesis of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00683] To a solution of 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.2 g, 0.53 mmol) in dichloromethane (5 mL) was added HATU (0.30 g, 0.8 mmol), *N,N*-dimethylpyridin-4-amine (0.003 g, 0.026 mmol) at 0 °C and the mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo. To the residue was added a solution of 3-aminobenzenesulfonamide (0.10 g, 0.63 mmol) in acetonitrile (5 mL) followed by heating at 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo, water was added, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 25-30% ethylacetate in hexane to afford 6,7-dichloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a yellow solid. Yield: 0.031 g, 11%; LRMS (ESI): Calcd $[M+H]^+$: 529.07, found:529.15.

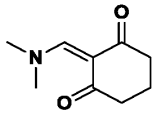
[00684] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.34 (s, 1H), 8.29 (s, 1H),8.17 (s, 1H), 7.85-7.82 (m, 2H), 7.60-7.55 (m, 2H), 7.42 (brs, 2H), 3.77-3.74 (m, 2H), 3.61 (t, J = 5.6 Hz, 2H), 2.43-2.35 (m, 2H), 1.99-1.95 (m, 2H), 1.89-1.88 (m, 2H).

Compound 83

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

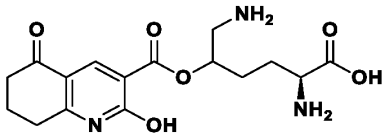


Synthesis of 2-((dimethylamino)methylene)cyclohexane-1,3-dione



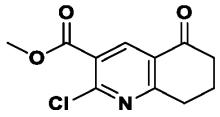
[00685] A mixture of cyclohexane-1,3-dione (10 g, 89 mmol) and 1-tert-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (17 g, 98 mmol) was heated at 80 °C for 24 hours. After reaction completion, the solvent was removed under reduced pressure to obtain the crude 2-((dimethylamino)methylene)cyclohexane-1,3-dione as brown liquid which was used in the next step without any further purification.

[00686] *Synthesis methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate*



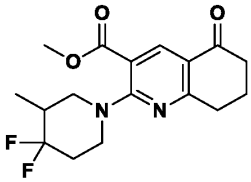
[00687] To a solution of crude 2-((dimethylamino)methylene)cyclohexane-1,3-dione (14 g, 84 mmol) in methanol (35 mL) was added methyl 2-cyanoacetate (10 g, 100.6 mmol) and heated at 80 °C for 18 hours. After reaction completion, the solvent was removed under reduced pressure and the residue was triturated with acetonitrile to afford methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate



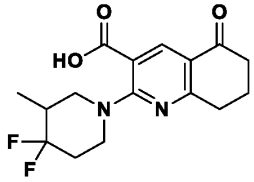
[00688] A solution of methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (5.0 g, 22.6 mmol) in phosphorus oxychloride (50 mL) was heated at 110 °C for 18 hours. After reaction completion, excess phosphorus oxychloride was distilled out, the residue was poured over crushed ice, neutralized with sodium carbonate solution, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient 50-70% ethyl acetate in hexane to afford methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as a yellow solid.

Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate



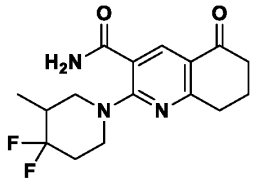
[00689] To a solution of methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.5 g, 2.1 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (0.86 g, 6.25 mmol) and 4,4-difluoro-3-methylpiperidine (0.34 g, 2.5 mmol) at room temperature then heated to 70 °C for 18 hours. After reaction completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as an off white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



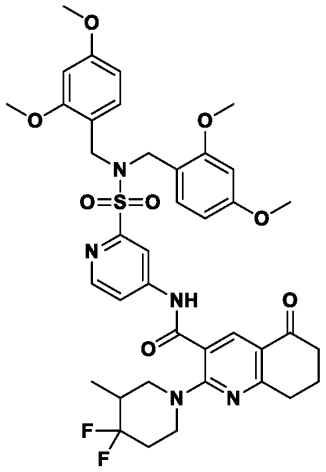
[00690] To a solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.4 g, 1.7 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added lithium hydroxide (0.14 g, 5.9 mmol) in water (10 mL) at room temperature and the reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide



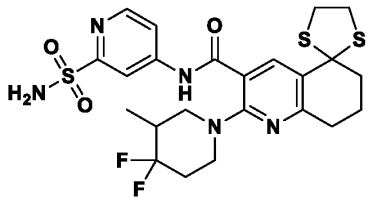
[00691] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.38 g 1.2 mmol) in *N,N*-dimethylformamide (5 mL) was added *N,N*-diisopropylethylamine (1.05 mL, 5.9 mmol), HATU (0.67 g, 1.76 mmol) and ammonium chloride (0.63 g, 11.7 mmol) at 0 °C. The reaction mixture was stirred for 16 hours at room temperature. After reaction completion, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-25 % ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide as a yellow solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00692] A solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.14 g, 0.43 mmol) in 1,4-dioxane (10 mL) were added cesium carbonate (0.28 g, 0.87 mmol) and 4-bromo-*N,N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.23 g, 0.43 mmol) at room temperature and the reaction mixture was degassed. BrettPhos Pd G3 (0.039 g, 0.043 mol) was added and the reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)-7,8-dihydro-6H-spiro[quinoline-5,2'-[1,3]dithiolane]-3-carboxamide



[00693] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.2

g, 0.26 mmol) in dichloromethane (8 mL) was added ethane-1,2-dithiol (0.021 mL, 0.26 mmol) and boron trifluoride etherate (0.095 mL, 0.77 mmol) at 0 °C. The reaction mixture was stirred room temperature for 18 hours. After reaction completion, the reaction mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-7,8-dihydro-6*H*-spiro[quinoline-5,2'-[1,3]dithiolane]-3-carboxamide as a white solid.

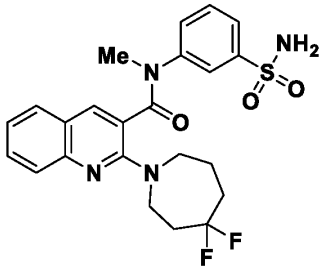
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-difluoro-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

To a solution of 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (0.15 g, 0.54 mmol) in dichloromethane (10 mL) was added pyridine hydrofluoride (0.75 mL, 0.135 mmol) dropwise at -78 °C. After stirring for 30 mins, a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-7,8-dihydro-6*H*-spiro[quinoline-5,2'-[1,3]dithiolane]-3-carboxamide (0.075 g, 0.135 mmol) in dichloromethane (10 mL) was added dropwise at -78 °C. The reaction mixture was stirred for 16 hours on the expiring cold bath. After reaction completion, the reaction mixture was quenched by sodium bicarbonate solution and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The reaction mixture was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-difluoro-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off-white solid. Yield: 0.009 g, 13%; LRMS (ESI): Calcd $[M+H]^+$: 502.15, found: 502.25.

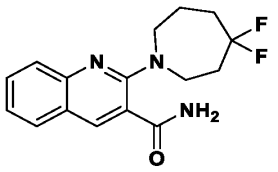
[00694] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1H), 8.61 (d, J = 5.6 Hz, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.98 (s, 1H), 7.85 (dd, J = 1.60, 5.2 Hz, 1H), 7.46 (br s, 2H), 3.85 (d, J = 13.60 Hz, 1H), 3.77 (d, J = 12 Hz, 1H), 3.18 (t, J = 11.60 Hz, 1H), 2.97 (t, J = 11.2 Hz, 1H), 2.92-2.81 (m, 2H), 2.33-2.28 (m, 2H), 2.13-2.07 (m, 2H), 1.95-1.84 (m, 3H), 0.89 (d, J = 6.8 Hz, 3H).

Compound 84

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-methyl-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

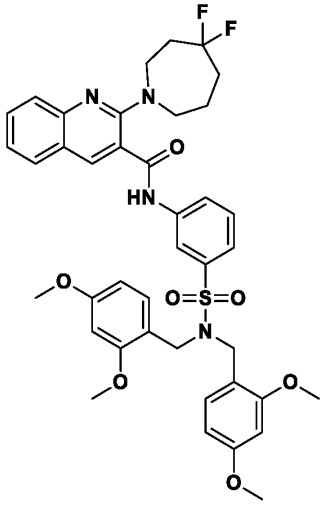


Synthesis of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



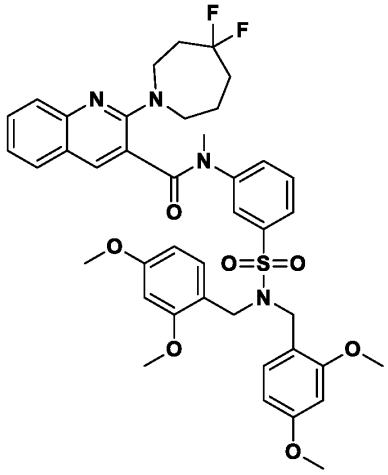
[00695] To a solution of 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxylic acid (1.0 g, 3.3 mmol) in dichloromethane (30 mL) was added (HATU (0.9 g, 4.9mmol) and ammonium carbonate (1.56 g, 193 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as an off-white solid.

Synthesis of N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00696] To a mixture of 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.6 g, 2 mmol) and 5-bromo-*N,N*-bis(2,4-dimethoxybenzyl) pyridine-3-sulfonamide (1.27 g, 2.35 mmol) in 1,4-dioxane (20 mL) was added cesium carbonate (1.28 g, 3.93 mmol) at room temperature. The reaction mixture was degassed with nitrogen, then BrettPhos Pd G3 (0.17 g, 0.2 mmol) was added and the reaction mixture was heated to 100 °C and stirred for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

Synthesis of N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)-N-methylquinoline-3-carboxamide



[00697] To a solution of *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (1.0 g, 1.3 mmol) in tetrahydrofuran (30 mL) was added sodium hydride (0.26 g, 6.55 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Methyl iodide (1.12 g, 7.86 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexane to afford *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)-*N*-methylquinoline-3-carboxamide as an off-white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-methyl-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

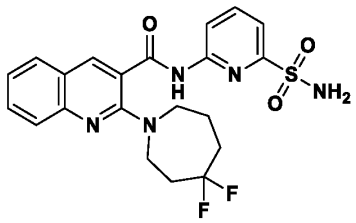
[00698] To a stirred solution of *N*-(3-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-2-(4,4-difluoroazepan-1-yl)-*N*-methylquinoline-3-carboxamide (0.80 g, 1.03 mmol) in dichloromethane (10 mL), was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After reaction completion, the excess trifluoroacetic acid was distilled out. The residue was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layers were separated, dried over anhydrous sodium sulfate, filtered, then concentrated in vacuo. The residue was purified by

flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-methyl-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as an off-white solid. Yield: 0.4 g, 82%; LRMS (ESI): Calcd $[M+H]^+$: 475.16, found: 475.25.

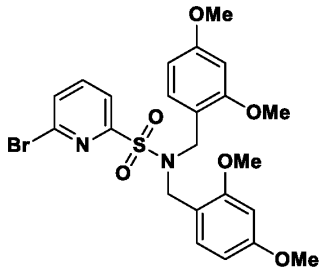
[00699] ^{1}H NMR (400 MHz, DMSO-d_6 (80 °C)): δ 8.18 (s, 1H), 7.7 4 (d, J = 7.2 Hz, 2H), 7.65-7.45 (m, 3H), 7.28-7.14 (m, 5H), 3.71-3.52 (m, 4H), 3.41 (s, 3H), 2.36-2.32 (m, 2H), 2.32-2.02 (m, 2H), 1.89-1.81 (m, 2H).

Compound 85

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(6-sulfamoylpyridin-2-yl) quinoline-3-carboxamide

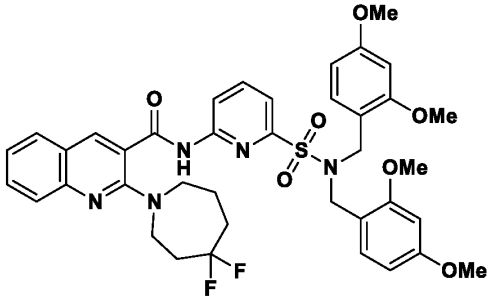


Synthesis of 6-bromo-N,N-bis(2,4-dimethoxybenzyl) pyridine-2-sulfonamide



[00700] To a solution of 6-bromopyridine-2-sulfonyl chloride (0.50 g, 1.95 mmol) in dichloromethane (5 mL) was added bis(2,4-dimethoxybenzyl) amine (0.74 g, 2.3 mmol) and diisopropylethylamine (1 mL, 5.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC. After completion of reaction, the crude mass was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 6-bromo-*N,N*-bis(2,4-dimethoxybenzyl) pyridine-2-sulfonamide as an off-white solid.

Synthesis of N-(6-(N,N-bis(2,4-dimethoxybenzyl) sulfamoyl) pyridin-2-yl)-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide



[00701] To a solution of 6-bromo-*N,N*-bis(2,4-dimethoxybenzyl) pyridine-2-sulfonamide (0.53 g, 0.98 mmol) and 2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.25 g, 0.82 mmol) in 1, 4-dioxane (2.5 mL), cesium carbonate (0.8 g, 2.46 mmol) was added. The reaction mixture was degassed with nitrogen gas for 20 min then BrettPhos Pd G3 (0.074 g, 0.08 mmol) was added under positive nitrogen pressure. The reaction mixture was heated at 100 °C for 24 hours under nitrogen atmosphere. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The crude material was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(6-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-2-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

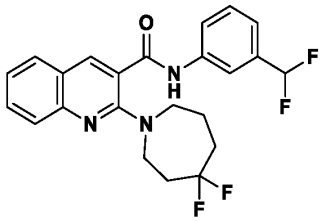
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(6-sulfamoylpyridin-2-yl) quinoline-3-carboxamide

[00702] A stirred solution of *N*-(6-(*N,N*-bis(2,4-dimethoxybenzyl) sulfamoyl) pyridin-2-yl)-2-(4,4-difluoroazepan-1-yl) quinoline-3-carboxamide (0.20 g, 0.26 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (TFA) (2 mL) at 0 °C and the reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the excess trifluoroacetic acid was removed in vacuo. The residue thus obtained was dissolved in dichloromethane and washed with sodium bicarbonate solution. The organic layers were separated, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude material which was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(6-sulfamoylpyridin-2-yl)quinoline-3-carboxamide as an off-white solid. LRMS (ESI): Calcd $[M+H]^+$: 462.14, found: 461.95.

[00703] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.35 (d, J = 8 Hz, 1H), 8.32 (brs, 1H), 8.13 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 4 Hz, 2H), 7.43 (brs, 2H), 7.31-7.27 (m, 1H), 3.75-3.73 (m, 2H), 3.57 (t, J = 6 Hz, 2H), 2.42-2.38 (m, 2H), 2.02-1.99 (m, 2H), 1.96-1.90 (m, 2H).

Compound 86

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-[3-(difluoromethyl)phenyl]quinoline-3-carboxamide



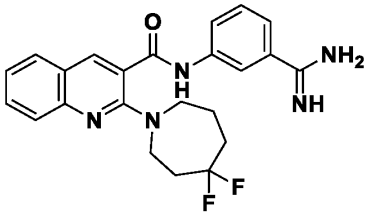
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-[3-(difluoromethyl)phenyl]quinoline-3-carboxamide

[00704] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.1 g, 0.33 mmol) in *N,N*-dimethylformamide (2 mL), was added (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.19 g, 0.49 mmol) and ethylbis(propan-2-yl)amine (0.13 g, 0.98 mmol) at 0 °C and the mixture was stirred at same temperature for 15 minutes. Afterwards, a solution of 3-(difluoromethyl)aniline (0.056 g, 0.039 mmol) in *N,N*-dimethylformamide (1 mL) was added and the reaction mixture was stirred for 16 hours at room temperature. After the reaction's completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated and the resultant crude product was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-[3-(difluoromethyl)phenyl]quinoline-3-carboxamide as a pale yellow solid. LRMS (ESI): Calcd $[M+H]^+$: 432.17, found: 432.00.

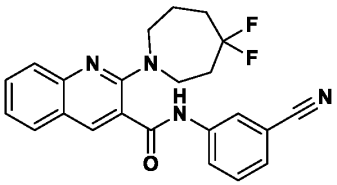
[00705] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.33 (s, 1H), 8.03 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.64-7.61 (m, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.06-7.93 (m, 1H), 7.32-7.28 (m, 2H), 3.76-3.75 (m, 2H), 3.62-3.59 (m, 2H), 2.40-2.30 (m, 2H), 2.10-1.90 (m, 2H), 1.89-1.88 (m, 2H).

Compound 87

Synthesis of N-(3-carbamimidoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of N-(3-cyanophenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00706] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.2 g, 0.65 mmol) in dichloromethane (4 mL) was added HATU (0.37 g, 0.98 mmol) and *N,N*-dimethylpyridine-4-amine (0.39 g, 0.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved into acetonitrile (4 mL) and 3-aminobenzonitrile (0.92 g, 0.78 mmol) was added at room temperature. The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexanes to afford *N*-(3-cyanophenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a brown solid.

Synthesis of N-(3-carbamimidoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

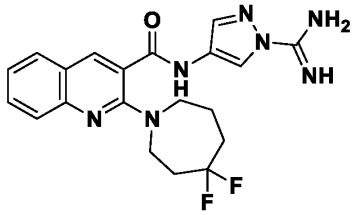
[00707] To *N*-(3-cyanophenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.17 g, 0.418 mmol) was added lithium bis(trimethylsilyl)amide (1.7 mL, 1.0 M in THF) and the reaction mixture was stirred for 16 hours at room temperature. After reaction completion, methanolic hydrochloric acid (1.7 mL) was added and the reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the

crude mixture was purified through reversed phase prep-HPLC to afford *N*-(3-carbamimidoylphenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white solid. Yield: 0.069 g, 38%; LRMS (ESI): Calcd $[M+H]^+$: 424.19, found: 424.25.

[00708] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.35 (s, 2H), 8.99 (s, 2H), 8.29 (s, 1H), 8.23 (t, J = 2.0 Hz, 1H), 7.94 (d, J = 5.2 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.65-7.60 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 3.77-3.74 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 2.42-2.38 (m, 2H), 2.03-1.97 (m, 2H), 1.90-1.88 (m, 2H).

Compound 88

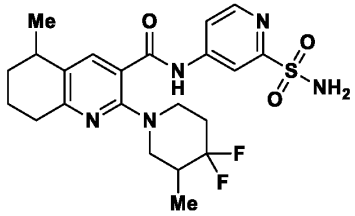
Synthesis of N-(1-carbamimidoyl-1H-pyrazol-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



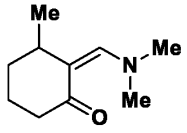
[00709] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 7.98-780 (m, 2H), 7.63-7.46 (m, 2H), 7.32-7.28 (m, 1H), 7.26-7.01 (br s, 1H), 3.73-3.70 (m, 2H), 3.57 (t, J = 6.0 Hz, 2H), 2.45-2.35 (m, 2H), 2.06-1.96 (m, 2H), 1.90-1.87 (m, 2H). LRMS (ESI): Calcd $[M+H]^+$: 414.18, found: 414.30.

Compound 89

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



Synthesis of (Z)-2-((dimethylamino)methylene)-3-methylcyclohexan-1-one



[00710] A mixture of 3-methylcyclohexan-1-one (10.0 g, 89.28 mmol) and [(tert-butoxy)(dimethylamino)methyl]dimethylamine (17.1 g, 98.2 mmol) was heated at 100 °C for 18 hours. After completion of reaction, the reaction mixture was concentrated under vacuum to afford a mixture of (*Z*)-2-((dimethylamino)methylene)-3-methylcyclohexan-1-one as a brown liquid. The crude mixture was carried forward into next step without purification.

Synthesis of methyl 2-hydroxy-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate

[00711] To a stirred solution of crude (*Z*)-2-((dimethylamino)methylene)-3-methylcyclohexan-1-one in methanol (70 mL) was added methyl 2-cyanoacetate (11 g, 112 mmol) and the resulting mixture was heated at 80 °C for 24 hours. After completion of reaction, solvent was evaporated under reduced pressure to obtain the crude residue which was suspended in acetonitrile and stirred at room temperature for 10 minutes. The resulting precipitate formed was filtered and washed with acetonitrile then dried under vacuum to afford a mixture of methyl 2-hydroxy-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid which was used as such into next step without purification.

Synthesis of methyl 2-chloro-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate

[00712] Phosphoryl chloride (80 mL) was added dropwise to a round bottom flask containing (8.0 g, 36.2 mmol) at 0-5°C. The reaction mixture was slowly warmed to room temperature and then heated at 110 °C for 18 hours. After completion of reaction, excess of phosphoryl chloride was evaporated and the residue was poured over ice, neutralized with saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated under vacuum to afford the crude compound which was purified by reversed phase prep-HPLC to obtained methyl 2-chloro-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate

[00713] To a stirred solution of methyl 2-chloro-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.50 g, 2.1 mmol) in *N*-methyl-2-pyrrolidone (2.5 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.42 g, 2.50 mmol) and *N,N*-diisopropylethyl amine (1.27 g, 10.45 mmol) was added at 0-5 °C. The resulting mixture was slowly warmed to room temperature and then heated at 110 °C for 16 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous

sodium sulfate and concentrated to afford the crude residue which was purified by a flash column chromatography with a gradient of 3-5% ethyl acetate in hexane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid

[00714] To a stirred solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.18 g, 0.53 mmol) in methanol (1.8 mL) and tetrahydrofuran (1.8 mL) was added lithium hydroxide (0.076 g, 3.19 mmol) and water (1.8 mL). The resulting mixture was stirred at room temperature for 24 hours. After completion of reaction, the reaction mixture was concentrated. The resulting residue was acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 70-80% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00715] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.17 g, 0.61 mmol) in dichloromethane (1.7 mL) was added [(dimethylamino)({3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy})methylidene]dimethylazanium hexafluoro-λ^5-phosphanuide (HATU) (0.35 g, 0.92 mmol) and ammonium carbonate (0.59 g, 6.1 mmol) at 0-5 ^oC. The resulting reaction mixture was slowly warmed to room temperature and stirred for 12 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography with a gradient of 60-65% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N, N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00716] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.10 g, 0.31 mmol) in 1,4-dioxane (3.1 mL), was added cesium carbonate (0.20 g, 0.62 mmol), BrettPhos Pd G3 (0.03 g, 0.031 mmol) and 4-bromo-*N*,*N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.17 g, 0.31 mmol) under nitrogen atmosphere and the reaction mixture was heated at 100 °C for 24 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

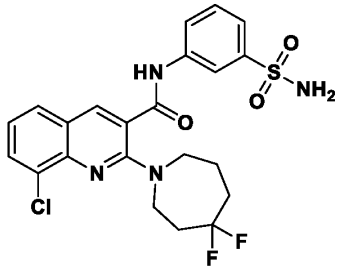
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00717] To a stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.20 g, 0.26 mmol) in dichloromethane (2.6 mL) was added trifluoroacetic acid (TFA) (0.8 mL) at 0-5 °C. The resulting mixture was stirred at room temperature for 12 hours. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product. The crude product was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-methyl-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as white solid. LRMS (ESI): Calcd $[M+H]^+$: 480.19, found: 480.25.

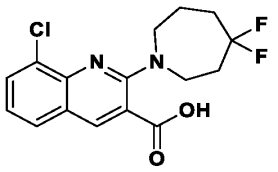
[00718] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.60 (d, J = 5.6 Hz, 1H), 8.36 (s, 1H), 7.81-7.80 (m, 1H), 7.70 (s, 1H), 7.44 (s, 2H), 3.63-3.54 (m, 2H), 3.09-3.03 (m, 1H), 2.88-2.70 (m, 4H), 2.14-2.07 (m, 2H), 1.89-1.86 (m, 3H), 1.74-1.68 (m, 1H), 1.51-1.43 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.91-0.90 (m, 3H).

Compound 90

Synthesis of 8-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

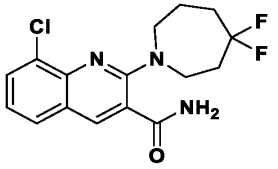


Synthesis of 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid



[00719] To a solution of 2,8-dichloroquinoline-3-carboxylic acid (0.45 g, 1.8 mmol) in *N,N*-dimethylformamide (5 mL) was added 4,4-difluoroazepane hydrochloride (0.47 g, 2.8 mmol) and potassium carbonate (1.2 g, 9.0 mmol). The mixture was heated at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with ice-cold water followed by acidification with 1*N* hydrochloric acid and extraction with ethyl acetate. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid as a white solid.

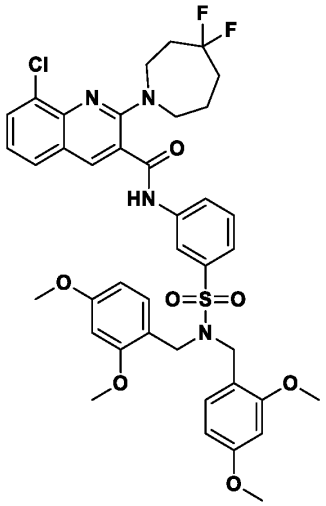
Synthesis of 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00720] To a solution of 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.3 g, 0.88 mmol) in *N,N*-dimethylformamide (5 mL) was added HATU (0.5 g, 1.3 mmol), *N,N*-diisopropylethylamine (0.8 mL, 4.4 mmol), ammonium chloride (0.46 g, 8.8 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl

acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white solid.

Synthesis of N-(3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00721] To a solution of 8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.25 g, 0.7 mmol) in 1,4-dioxane (5 mL) was added 3-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (0.47 g, 0.88 mmol), cesium carbonate (0.45 g, 1.4 mmol) and RuPhos Pd G3 (0.05 g, 0.07 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(3-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white solid.

Synthesis of 8-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

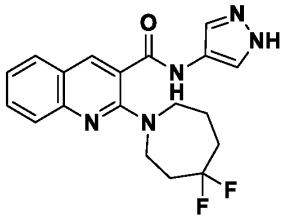
[00722] To a solution of *N*-(3-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)phenyl)-8-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.10 g, 0.12 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at

room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was dissolved into ethyl acetate and washed with saturated solution of sodium bicarbonate. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford 8-chloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a white solid. Yield: 0.03 g, 48%; LRMS (ESI): Calcd $[M+H]^+$: 495.11, found: 495.20.

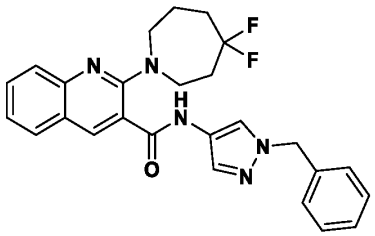
[00723] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (br s, 1H), 8.40 (s, 1H), 8.30 (t, J = 5.2 Hz, 1H), 7.87-7.80 (m, 3H), 7.58-7.57 (m, 2H), 7.42 (s, 2H), 7.27 (t, J = 1.6 Hz, 1H), 4.19-3.93 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.49-2.43 (m, 2H), 2.07-1.90 (m, 4H).

Compound 91

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(1H-pyrazol-4-yl) quinoline-3-carboxamide



Synthesis of N-(1-benzyl-1H-pyrazol-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00724] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.50 g, 1.6 mmol) in *N,N*-dimethylformamide (2.5 mL) was added 1-benzyl-1*H*-pyrazol-4-amine (0.34 g, 2 mmol). *N,N*-Diisopropylethylamine (0.9 mL, 4.9 mmol) and HATU (0.93 g, 2.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography

with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(1-benzyl-1*H*-pyrazol-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

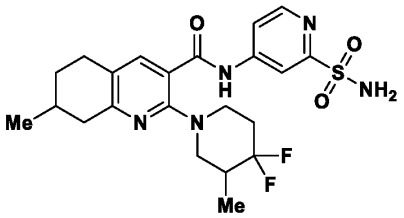
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(1H-pyrazol-4-yl)quinoline-3-carboxamide

[00725] To a stirred solution *N*-(1-benzyl-1*H*-pyrazol-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.50 g, 1.2 mmol) in ethanol (5 mL) was added cyclohexene (0.2 mL 2.4 mmol) and 20% palladium hydroxide on carbon (0.25 mg) at room temperature. The reaction mixture was stirred at 80 °C for 12 hours. After reaction completion, the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(1*H*-pyrazol-4-yl)quinoline-3-carboxamide as an off-white solid. Yield: 0.250 g, 62%; LRMS (ESI): Calcd $[M+H]^+$: 372.16, found: 372.20.

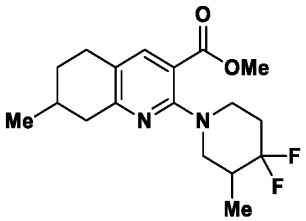
[00726] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (br s, 1H), 10.65 (s, 1H), 8.22 (s, 1H), 7.96 (br s, 1H), 7.81 (d, J = 8 Hz, 1H), 7.61-7.58 (m, 3H), 7.30-7.26 (m, 1H), 3.72-3.70 (m, 2H), 3.57 (t, J = 8 Hz, 2H), 2.40-2.32 (m, 2H), 2.07-1.96 (m, 2H), 1.87-1.85 (m, 2H).

Compound 92

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



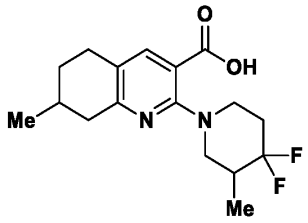
Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00727] To a stirred solution of methyl 2-chloro-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.5 g, 2.1 mmol) and 4,4-difluoro-3-methylpiperidine (0.32 g, 2.5 mmol) in *N*-methyl-2-pyrrolidone (2.5 mL), ethylbis(propan-2-yl)amine (1.3 g, 10.5 mmol) was added at

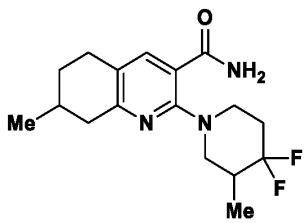
0-5 °C. The reaction mixture was slowly warmed to room temperature and then heated at 110 °C for 16 hours. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude product which was purified by flash column chromatography with a gradient of 3-5% ethyl acetate in hexane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



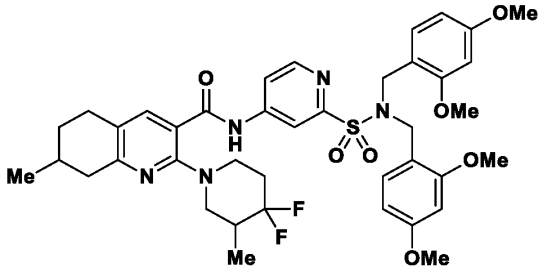
[00728] To a stirred solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.25 g, 0.74 mmol) in methanol (2.5 mL) and tetrahydrofuran (2.5 mL) was added a solution of lithium hydroxide (0.11 g, 4.4 mmol) in water (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. After completion of reaction, the reaction mixture was concentrated. The residue was neutralized with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to afford the crude product which was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00729] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.23 g, 0.71 mmol) in dichloromethane (2.3 mL), [(dimethylamino)({3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium hexafluoro-λ^5-phosphanuide (HATU) (0.40 g, 1.0 mmol) and ammonium carbonate (0.68 g, 7.1 mmol) was added at 0 °C. The resulting mixture was slowly warmed to room temperature and stirred for 12 hours. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product which was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00730] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.16 g, 0.49 mmol) in 1,4-dioxane (1.6 mL) was added cesium carbonate (0.32 g, 0.99 mmol), BrettPhos Pd G3 (0.04 g, 0.05 mmol) and 4-bromo-*N*,*N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.27 g, 0.49 mmol) at 0-5 °C under nitrogen atmosphere. The resulting mixture was slowly warmed to room temperature and then heated at 100 °C for 24 hours. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure and the crude residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

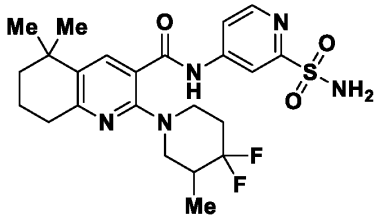
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00731] To a stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.35 g, 0.45 mmol) in dichloromethane (3.5 mL) was added trifluoroacetic acid (1.8 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 hours. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to afford the crude residue which was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. LRMS (ESI): Calcd $[M+H]^+$: 480.19, found: 480.30.

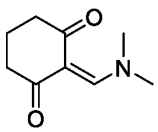
[00732] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.36-835 (m, 1H), 7.81-7.79 (m, 1H), 7.61 (s, 1H), 7.44 (s, 2H), 3.62-3.54 (m, 2H), 3.09-3.03 (m, 1H), 2.85-2.66 (m, 4H), 2.39-2.35 (m, 1H), 2.13-2.07 (m, 2H), 1.87-1.83 (m, 3H), 1.36-1.32 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.90-0.88 (m, 3H).

Compound 93

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-dimethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



Synthesis of 2-((dimethylamino)methylene)cyclohexane-1,3-dione



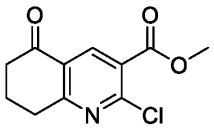
[00733] To a stirred solution of cyclohexane-1,3-dione (10 g, 89 mmol) in toluene (20 mL), 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetramethylmethanediamine (18.7 g, 107 mmol) was added and the reaction mixture was heated at 80 °C for 24 hours. After reaction completion, the reaction

mixture was concentrated to afford crude 2-((dimethylamino)methylene)cyclohexane-1,3-dione as a brown liquid which was used in the next step without further purification.

Synthesis of methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate

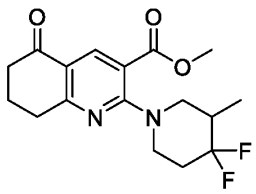
[00734] To a stirred solution of 2-((dimethylamino)methylene)cyclohexane-1,3-dione (15 g, 90 mmol) in methanol (35 mL), methyl 2-cyanoacetate (10.7 g, 108 mmol) was added and the reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was triturated with acetonitrile to afford methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as a light yellow solid.

Synthesis of methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00735] Phosphoryl trichloride (20 mL) was added dropwise to a round bottom flask containing methyl 2-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (2.0 g, 9.1 mmol) at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 110 °C for 18 hours. After reaction completion, the reaction mixture was cooled to room temperature, poured into crushed ice, neutralized with saturated sodium bicarbonate, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

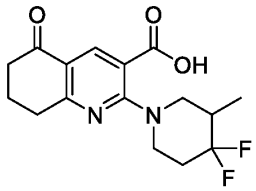
Synthesis of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate



[00736] To a stirred solution of methyl 2-chloro-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.2 g, 0.83 mmol) in *N*-methyl-2-pyrrolidone (3 mL), 4,4-difluoro-3-methylpiperidine hydrochloride (0.205 g, 1.2 mmol) and *N,N*-diisopropylethylamine (0.54 g, 4.2 mmol) were added and the reaction mixture was heated at 110 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water,

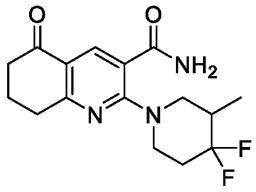
then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid



[00737] To a stirred solution of methyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (0.15 g, 0.45 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) a solution of lithium hydroxide (0.063 g, 2.7 mmol) in water (10 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated and the resulting aqueous solution was neutralized with 1N hydrochloric acid then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulphate, filtered, then concentrated. The residue was triturated with *n*-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid as a white solid.

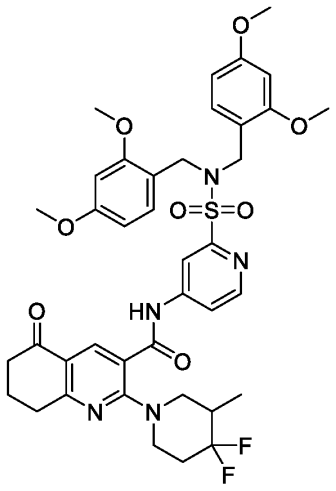
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00738] To a stirred suspension of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.1 g, 0.32 mmol) in dichloromethane (10 mL), HATU (0.18 g, 0.46 mmol) and ammonium carbonate (0.3 g, 3.1 mmol) were added at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water and extracted with dichloromethane. The organic

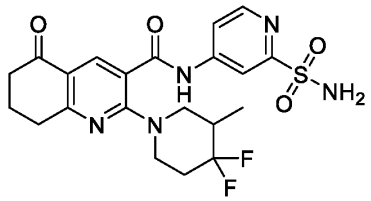
layers were combined, washed with brine, dried over anhydrous sodium sulphate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00739] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.1 g, 0.31 mmol) in 1,4-dioxane (5 mL) was added cesium carbonate (0.20 g, 0.62 mmol) and 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.17 g, 0.31 mmol). The reaction mixture was degassed for 10 minutes. BrettPhos Pd G3 (0.028 g, 0.03 mmol) was added the reaction mixture stirred at 100 °C for 24 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with ethyl acetate. The organic layers were washed with brine, dried over sodium sulphate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00740] To a stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.07 g) in dichloromethane (10 mL), trifluoroacetic acid (0.4 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic layers were washed with brine, dried over sodium sulphate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a pale yellow solid.

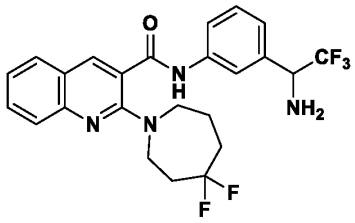
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-dimethyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

[00741] To a stirred solution of titanium tetrachloride (0.079 g, 0.42 mmol) in dichloromethane (10 mL), dimethylzinc (0.04 g, 0.42 mmol) was added dropwise at -30 °C and the resulting mixture was stirred for 10 minutes. To the reaction mixture was added a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-oxo-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.1 g, 0.21 mmol) in dichloromethane (10 mL) dropwise at -30 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulphate, filtered, then concentrated. The residue was purified by preparative HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,5-dimethyl-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a pale yellow solid. Yield: 0.005 g, 9%; LRMS (ESI): Calcd $[M+H]^+$: 494.20 found: 494.30.

[00742] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.36 (s, 1H), 8.32 (d, J = 3.6 Hz, 1H), 7.81 (s, 1H), 7.45 (br s, 2H), 3.74-3.60 (m, 2H), 3.05 (t, J = 10 Hz, 1H), 2.82 (t, J = 11.6 Hz, 1H), 2.30-2.21 (br s, 1H), 2.09-1.98 (m, 2H), 1.92-1.81 (m, 3H), 1.68-1.61 (m, 3H), 1.23 (s, 6H), 0.87 (d, J = 12.4 Hz, 3H).

Compound 94

Synthesis of N-[3-(1-amino-2,2,2-trifluoroethyl)phenyl]-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



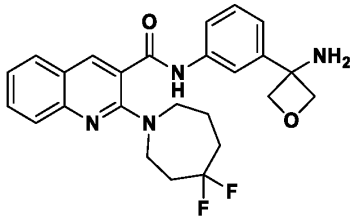
Synthesis of N-[3-(1-amino-2,2,2-trifluoroethyl)phenyl]-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00743] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.2 g, 0.66 mmol) in 1,4-dioxane (5 mL), cesium carbonate (0.43g, 1.31 mmol), Pd BrettPhos G3 (0.06 g, 0.065 mmol) and 1-(3-bromophenyl)-2,2,2-trifluoroethan-1-amine hydrochloride (0.19 g, 0.66 mmol) were added at room temperature then heated at 100 °C for 24 hours under nitrogen atmosphere. After the reaction's completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product which was purified by reversed phase prep-HPLC to afford *N*-[3-(1-amino-2,2,2-trifluoroethyl)phenyl]-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a pale yellow solid. LRMS (ESI): Calcd $[M+H]^+$: 479.19, found: 479.40.

[00744] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.29 (s, 1H), 7.84-7.82 (m, 2H), 7.74 (d, J = 80 Hz, 1H), 7.64-7.62 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.32-7.29 (m, 1H), 7.29-7.25 (m, 1H), 4.50-4.46 (m, 1H), 3.76-3.75 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 2.50-2.49 (m, 2H), 2.45-2.32 (m, 2H), 2.02-1.96 (m, 2H), 1.89-1.88 (m, 2H).

Compound 95

Synthesis of N-(3-(3-aminooxetan-3-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

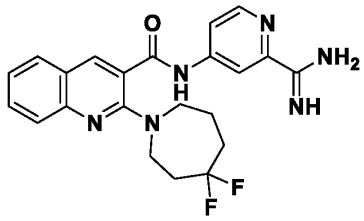


[00745] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.25 g, 0.8 mmol) in 1,4-dioxane (3 mL) was added 3-(3-bromophenyl)oxetan-3-amine hydrochloride (0.24 g, 0.92 mmol), cesium carbonate (0.52 g, 1.6 mmol) and BrettPhos Pd G3 (0.07 g, 0.08 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(3-(3-aminooxetan-3-yl)phenyl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white solid. Yield: 0.011 g, 3%; LRMS (ESI): Calcd $[M+H]^+$: 453.21 found: 453.20.

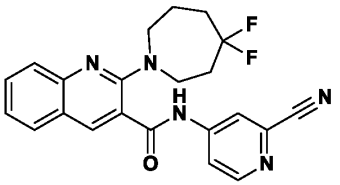
[00746] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.28 (s, 1H), 7.91 (t, J = 1.2 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.73-7.70 (m, 1H), 7.64-7.59 (m, 2H), 7.39-7.30 (m, 3H), 4.88-4.65 (m, 4H), 3.77-3.74 (m, 2H), 3.63 (t, J = 5.6 Hz, 2H), 2.41-2.37 (m, 2H), 2.05-2.00 (m, 2H), 1.97-1.87 (m, 2H).

Compound 96

Synthesis of N-(2-carbamimidoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



Synthesis of N-(2-cyanopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00747] To a solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.15 g, 0.5 mmol) in 1,4-dioxane (3 mL) was added 4-bromopicolinonitrile (0.10 g, 0.59 mmol), cesium carbonate (0.31 g, 0.98 mmol) and BrettPhos Pd G3 (0.04 g, 0.05 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the solvent was removed in vacuo and the residue was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford *N*-(2-cyanopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid.

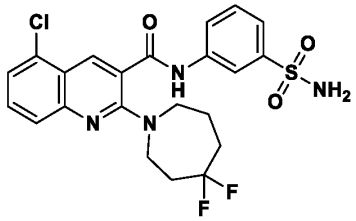
Synthesis of N-(2-carbamimidoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00748] A solution of *N*-(2-cyanopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.10 g, 0.24 mmol) in lithium bis(trimethylsilyl)amide (1M in THF) (1.2 ml, 1.2 mmol) was heated at 60 °C for 12 hours. After cooling the reaction mixture, 1M methanolic hydrochloride solution (0.5 mL) was added and the reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo. The residue was purified through reversed phase prep-HPLC to afford *N*-(2-carbamimidoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a yellow solid. Yield: 0.04 g, 38%; LRMS (ESI): Calcd $[M+H]^+$: 425.19 found: 425.20.

[00749] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 9.55 (s, 1H), 9.21 (s, 2H), 8.73 (d, J = 5.6 Hz, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 7.89-7.84 (m, 2H), 7.66-7.65 (m, 2H), 7.35-7.31 (m, 1H), 3.75-3.55 (m, 2H), 3.57 (t, J = 10.8 Hz, 2H), 2.49-2.45 (m, 2H), 2.02-1.99 (m, 2H), 1.96-1.88 (m, 2H).

Compound 97

Synthesis of 5-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

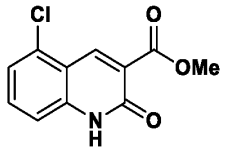


Synthesis of 2-amino-6-chlorobenzaldehyde



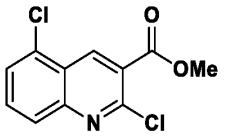
[00750] To a stirred solution of 2-chloro-6-nitrobenzaldehyde (2.5 g, 13.5 mmol) in ethanol (50 mL) was added iron powder (7.88 g, 134.7 mmol) and conc. HCl (1 mL) at room temperature and resultant mixture was refluxed for 2 hours. After completion of reaction, the reaction mixture was filtered through celite and solvent was removed in vacuo. The residue was diluted with water and then extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product which was purified through trituration with n-pentane to afford 2-amino-6-chlorobenzaldehyde as a pale yellow solid.

Synthesis of methyl 5-chloro-2-hydroxyquinoline-3-carboxylate



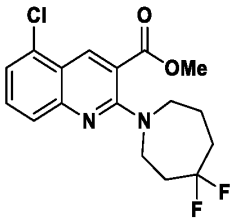
[00751] To a stirred solution of 2-amino-6-chlorobenzaldehyde (1.7 g, 10.9 mmol) in ethanol (30 mL) was added diethyl malonate (4.54 mL, 32.8 mmol) and piperidine (3.3 mL, 32.8 mmol) at room temperature and slowly heated to 80 °C for 12 hours. After completion of reaction, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and triturated with diethyl ether and n-pentane to afford methyl 5-chloro-2-hydroxyquinoline-3-carboxylate as an off-white solid.

Synthesis of methyl 2,5-dichloroquinoline-3-carboxylate



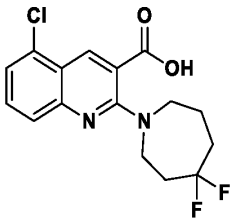
[00752] A mixture of methyl 5-chloro-2-hydroxyquinoline-3-carboxylate (1.8 g, 7.7 mmol) and phosphorous oxychloride ($POCl_3$) (18 mL) was heated to 110°C for 12 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched with saturated sodium bicarbonate solution followed by extraction with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and triturated with n-pentane to afford methyl 2,5-dichloroquinoline-3-carboxylate as an off-white solid.

Synthesis of methyl 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate



[00753] To a solution of methyl 2,5-dichloroquinoline-3-carboxylate (0.6 g, 2.34 mmol) in *N*,*N*-dimethylformamide (12 mL) was added 4,4-difluoroazepane hydrogen chloride (0.60 g, 3.5 mmol) and cesium carbonate (3.04 g, 9.36 mmol). The mixture was heated at 100 °C for 24 hours under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of reaction, the crude mixture was diluted with water then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure and the residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexane to afford methyl 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate as a yellow solid.

Synthesis of 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid



[00754] To a stirred solution of methyl 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylate (0.32 g, 0.90 mmol) in methanol (10 mL), THF (10 mL) was added solution of lithium hydroxide monohydrate (0.16 g, 3.6 mmol) in water (10 mL) at room temperature and stirred for 12 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed in vacuo and the residue was diluted with water then acidified with 1*N* hydrochloric acid solution and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was triturated with n-pentane and diethyl ether to afford 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid as a brown solid.

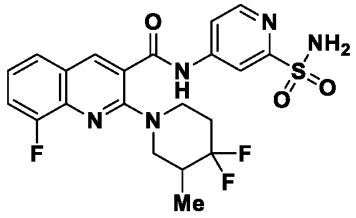
Synthesis of 5-chloro-2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00755] To a stirred solution of 5-chloro-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (0.23 g, 0.67 mmol) in dichloromethane (5 mL) was added 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-Oxide Hexafluorophosphate (HATU) (0.38 g, 1.02 mmol) and 4-DMAP (0.04 g, 0.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. The progress of reaction was monitored by TLC and LCMS. After completion of reaction, the solvent was removed in vacuo and the residue was diluted with acetonitrile (10 mL) and to this solution 3-aminobenzenesulfonamide (0.14 g, 0.81 mmol) was added followed by heating at 90 °C for 16 h. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography with a gradient of 60-70% ethyl acetate in hexane to afford 5-chloro-2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as an off-white solid. LRMS (ESI): Calcd $[M+H]^+$: 495.11, found: 495.15.

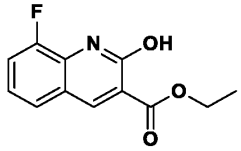
[00756] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 8.39 (s, 1H), 8.30 (s, 1H), 7.88 (d, J = 6.4 Hz, 1H), 7.62-7.56 (m, 4H), 7.46-7.44 (m, 1H), 7.41 (s, 2H), 3.78-3.72 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.40-2,32 (m, 2H), 2.07-1.99 (m, 2H), 1.91-1.98 (m, 2H).

Compound 98

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

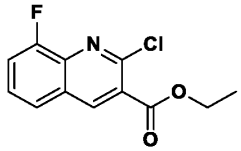


Synthesis of ethyl 8-fluoro-2-hydroxyquinoline-3-carboxylate



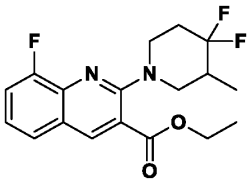
[00757] To a stirred solution of 2-amino-3-fluorobenzaldehyde (2.5 g, 18 mmol) in ethanol (50 mL) was added 1,3-diethyl propanedioate (5.5 mL, 36 mmol) and piperidine (0.9 mL, 9 mmol) at 0 °C. The mixture was heated at 80 °C and stirred for 18 hours. After reaction completion, the reaction mixture was cooled to room temperature and filtered. The solid precipitate obtained was washed with ethanol and hexane to afford ethyl 8-fluoro-2-hydroxyquinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-chloro-8-fluoroquinoline-3-carboxylate



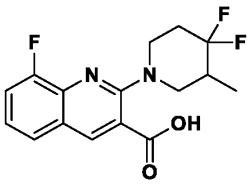
[00758] To a solution of ethyl 8-fluoro-2-hydroxyquinoline-3-carboxylate (1.0 g, 4.25 mmol) in acetonitrile (10 mL) was added phosphorus oxychloride (10 mL) at 0 °C. The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated to obtain the crude ethyl 2-chloro-8-fluoroquinoline-3-carboxylate as a white solid which was used directly into next step without purification.

Synthesis of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylate



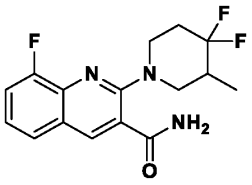
To a stirred solution of ethyl 2-chloro-8-fluoroquinoline-3-carboxylate (0.4 g, 1.6 mmol) in *N,N*-dimethylformamide (13.8 mL) was added potassium carbonate (0.65 g, 4.7 mmol) and 4,4-difluoro-3-methylpiperidine (0.32 g, 0.34 mmol) at room temperature. The reaction mixture was heated at 110 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylic acid



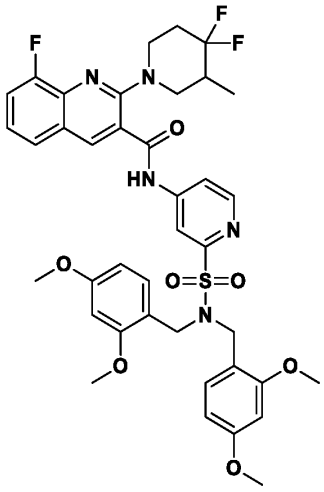
[00759] To a stirred solution of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylate (0.5 g, 1.4 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) was added a solution of lithium hydroxide (0.17 g, 7.1 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, organic solvents were removed under reduced pressure and the resulting aqueous solution was neutralized with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was triturated with pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide



[00760] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxylic acid (0.39 g, 1.2 mmol) in *N,N*-dimethylformamide (4 mL) was added HATU (0.69 g, 1.2 mmol), ethylbis(propan-2-yl)amine (1.05 mL, 6 mmol) and ammonium chloride (0.643 g, 12 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide



[00761] To a stirred solution 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide (0.3 g, 0.93 mmol) in 1,4-dioxane (10 mL) was added 4-bromo-*N,N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.60 g, 1.11 mmol) and cesium carbonate (0.61 g, 1.86 mmol) at room temperature and the reaction mixture was degassed. BrettPhos Pd G3 (0.084 g, 0.093 mmol) was added under nitrogen atmosphere. The reaction mixture was

heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide as a white solid.

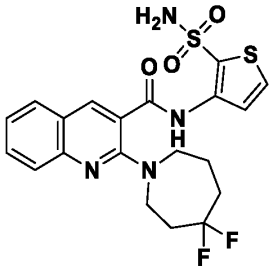
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00762] To a stirred solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoroquinoline-3-carboxamide (0.45 g, 0.64 mmol) in dichloromethane (4.5 mL), trifluoroacetic acid (2.2mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated sodium bicarbonate solution, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-8-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a white solid. Yield: 0.21 g, 76%; LRMS (ESI): Calcd $[M+H]^+$: 480.13 found: 480.15.

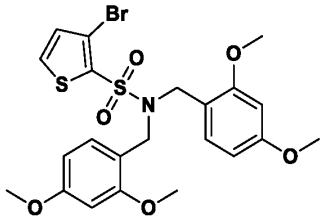
[00763] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (s, 1H), 8.65 (d, J = 5.6 Hz, 1H), 8.55 (d, J = 1.6 Hz, 1H), 8.36 (d, J = 1.6 Hz, 1H), 7.87 (dd, J = 5.6, 2.0 Hz, 1H), 7.75-7.74 (m, 1H), 7.58-7.53 (m, 1H), 7.49 (br s, 2H), 7.40-7.35 (m, 1H), 3.96-3.93 (m, 1H), 3.86-3.83 (m, 1H), 3.26-3.23 (m, 1H), 3.07-3.01 (m, 1H), 2.22-2.13 (m, 2H), 2.04-1.90 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H)

Compound 99

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

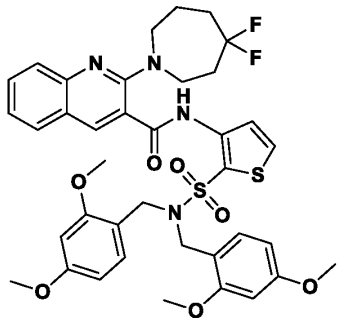


Synthesis of 3-bromo-N,N-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide



[00764] To a stirred solution of bis(2,4-dimethoxybenzyl)amine (0.24 g, 0.765 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (0.15 g, 1.15 mmol) and 3-bromothiophene-2-sulfonyl chloride (0.1 g, 0.38 mmol) were added at 0-5 °C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 12 hours. After reaction completion, ice-cold water was added followed by extraction with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford 3-bromo-*N,N*-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide



[00765] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.1 g, 0.33 mmol) in 1,4-dioxane (5 mL), cesium carbonate (0.213 g, 0.655 mmol), BrettPhos Pd G3 (0.029 g, 0.328 mmol) and 3-bromo-*N,N*-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide (0.18 g, 0.33 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and then heated to 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 60-70% ethyl

acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a white solid.

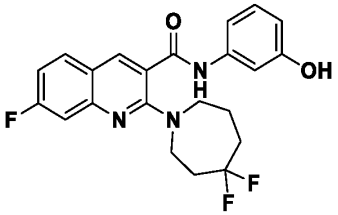
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(2-sulfamoylthiophen-3-yl)quinoline-3-carboxamide

[00766] To a stirred solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.17 g, 0.22 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.8 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(2-sulfamoylthiophen-3-yl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.038 g, 36.7%; LRMS (ESI): Calcd $[M+H]^+$: 467.10 found: 467.15.

[00767] ^{1}H NMR (400 MHz, DMSO-d_6): 10.06 (s, 1H), 8.42 (s, 1H), 7.87 (q, J = 5.2 Hz, 3H), 7.73 (s, 2H), 7.65 (d, J = 4.0 Hz, 2H), 7.36-7.32 (m, 1H), 3.73-3.72 (m, 2H), 3.57 (t, 5.6 Hz, 2H), 2.43-2.36 (m, 2H), 2.08-1.99 (m, 2H), 1.89-1.88 (m, 2H).

Compound 100

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-hydroxyphenyl) quinoline-3-carboxamide



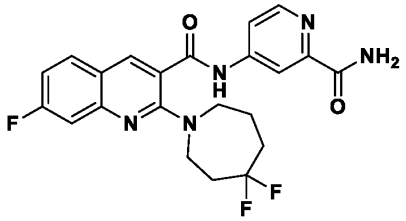
[00768] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.25 g, 0.77 mmol) in *N,N*-dimethylformamide (2.5 mL) was added 3-aminophenol (0.10 g, 0.93 mmol), *N,N*-Diisopropylethylamine (0.4 mL, 2.31 mmol) and HATU (0.44 g, 1.22 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography

with a gradient of 50-60% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(3-hydroxyphenyl)quinoline-3-carboxamide as a white solid. Yield: 0.035 g, 11%; LRMS (ESI): Calcd $[M+H]^+$: 416.16 found: 416.15.

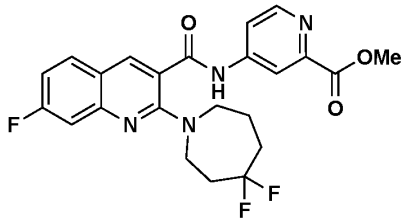
[00769] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.44 (br s, 1H), 8.29 (s, 1H), 7.93-7.89 (m, 1H), 7.33-7.30 (m, 2H), 7.21-7.19 (m, 1H), 7.18-7.06 (m, 2H), 6.52-6.50 (m, 1H), 3.76-3.74 (m, 2H), 3.62 (t, 2H), 2.49-2.34 (m, 2H), 2.07-2.04 (m, 2H), 1.99-1.88 (m, 4H).

Compound 101

Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



Synthesis of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate



[00770] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (26 mg, 0.08 mmol) in DCM (1 mL) was added oxalyl chloride (12.6 µL, 0.144 mmol) and 1 drop of DMF. The reaction mixture was stirred at room temperature for 15 minutes. A solution of methyl 4-aminopicolinate (12 mg, 0.08 mmol) and DIPEA (42 µL, 0.24 mmol) in DMF (1 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 96 hours. After reaction completion, the reaction mixture was purified by flash column chromatography using a gradient of ethyl acetate in hexanes to give methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate as a light yellow powder.

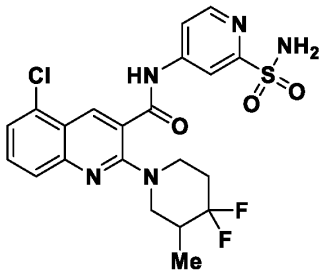
Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00771] A round bottom flask was charged with methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate (74 mg, 0.16 mmol) and 7M ammonia in methanol (10 mL). The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was concentrated and the residue was purified with reverse-phase HPLC to give N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a light yellow powder. Yield: 1.7 mg, 2.4%; LRMS (ESI): Calcd $[M+H]^+$: 444.16 found: 444.25.

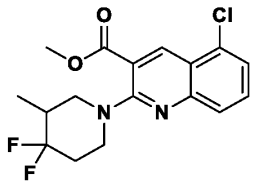
[00772] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.43 (s, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.14 – 8.09 (m, 1H), 7.97 – 7.87 (m, 2H), 7.69 – 7.63 (m, 1H), 7.34 (dd, J = 11.1, 2.6 Hz, 1H), 7.22 (td, J = 8.8, 2.6 Hz, 1H), 3.78 – 3.71 (m, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.41 – 2.36 (m, 2H), 2.03 – 1.94 (m, 2H), 1.92 – 1.84 (m, 2H).

Compound 102

Synthesis of 2-(3-amino-4,4-difluoropiperidin-1-yl)-5-chloro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide



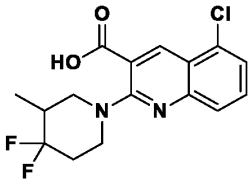
Synthesis of methyl 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylate



[00773] To a solution of methyl 2,5-dichloroquinoline-3-carboxylate (0.5 g, 2 mmol) in *N,N*-dimethylformamide (10 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.32 g, 2.34 mmol) and potassium carbonate (1.1 g, 7.8 mmol). The mixture was heated at 100 °C for 16 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography (10-20% ethyl acetate in hexane to

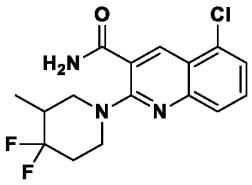
afford methyl 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylate as a white solid.

Synthesis of 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid



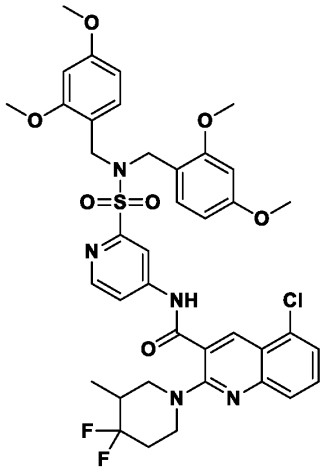
[00774] To a stirred solution of methyl 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylate (0.37 g, 1 mmol) in methanol (10 mL), tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.18 g, 4.2 mmol) in water (10 mL) at room temperature. The reaction mixture was stirred at 55 °C for 24 hours. After reaction completion, the solvent was removed in vacuo. The residue was diluted with ice-cold water followed by treatment with 1*N* hydrochloric acid to and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then filtered. The filtrate was concentrated and the residue was triturated with pentane and diethyl ether to afford 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid as an off-white solid.

Synthesis of 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide



[00775] To a solution of 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid (0.27 g, 0.79 mmol) in dichloromethane (20 mL) was added HATU (0.45 g, 1.19 mmol) and ammonium carbonate (0.75 g, 7.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was washed with brine and extracted with dichloromethane. The organic layers were dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide



[00776] To a solution of 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide (0.12 g, 0.35 mmol) in 1,4-dioxane (6 mL) was added 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.23 g, 0.42 mmol), cesium carbonate (0.35 g, 1.06 mmol) and RuPhos Pd G3 (0.06 g, 0.07 mmol) under nitrogen atmosphere. The reaction mixture was heated at 80 °C for 18 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide as a pale pink solid.

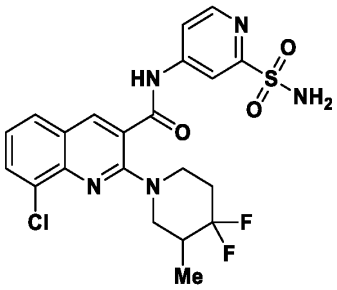
Synthesis of 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00777] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide (0.1 g, 0.13 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (3 mL) at 0 °C. The reaction mixture was brought from 0 °C to room temperature and stirred for 12 hours. After reaction completion, the solvent was removed under reduced pressure and the residue was purified by Prep-HPLC to afford 5-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as pale-yellow solid. Yield: 0.01 g, 16%; LRMS (ESI): Calcd $[M+H]^+$: 496.10 found: 496.20.

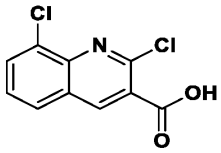
[00778] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.38 (br s, 1H), 8.65 (d, J = 5.2 Hz, 1H), 8.54 (s, 1H), 8.35 (s, 1H), 7.89 (d, J = 4.8 Hz, 1H), 7.73-7.67 (m, 2H), 7.56 (dd, J = 6.4, 1.6 Hz, 1H), 7.48 (br s, 2H), 3.96-3.85 (m, 2H), 3.27-3.24 (m, 2H), 3.06-3.00 (m, 1H), 2.33-2.21 (m, 2H), 1.96-1.90 (m, 1H), 0.93 (d, J = 5.2 Hz, 1H).

Compound 103

Synthesis of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

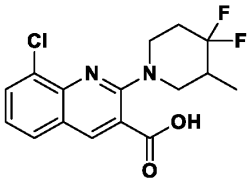


Synthesis of 2,8-dichloroquinoline-3-carboxylic acid



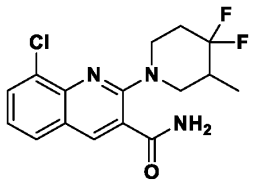
[00779] To a stirred solution of 2,8-dichloroquinoline-3-carbaldehyde (0.50 g, 2.2 mmol) in ethanol (5 mL) was added silver nitrate (0.6 g, 3.5 mmol) and a solution of sodium hydroxide (0.44 g, 11 mmol) in water (2.5 mL) at room temperature and stirred for 5 hours. After reaction completion, the mixture was filtered through a Celite pad and the solvent was removed under reduced pressure. The residue was diluted with water followed by acidification with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2,8-dichloroquinoline-3-carboxylic acid as a white solid.

Synthesis of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid



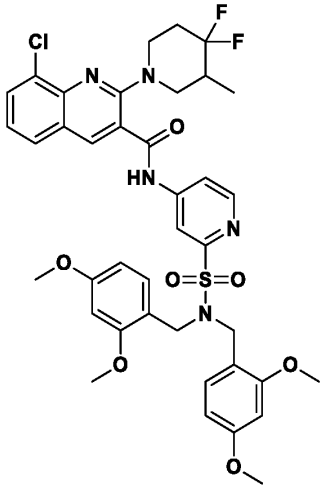
[00780] To a solution of 2,8-dichloroquinoline-3-carboxylic acid (0.45 g, 1.8 mmol) in *N,N*-dimethylformamide (5 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.47 g, 2.8 mmol) and potassium carbonate (1.2 g, 9.0 mmol). The mixture was heated at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with ice-cold water followed by acidification with 1*N* hydrochloric acid and extraction with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid as a white solid.

Synthesis of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide



[00781] To a solution of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxylic acid (0.3 g, 0.88 mmol) in *N,N*-dimethylformamide (5 mL) was added HATU (0.50 g, 1.32 mmol), *N,N*-diisopropylethylamine (0.8 mL, 4.4 mmol) and ammonium chloride (0.46 g, 8.8 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide



[00782] To a solution of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide (0.25 g, 0.7 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.47 g, 0.88 mmol), cesium carbonate (0.45 g, 1.4 mmol) and RuPhos Pd G3 (0.05 g, 0.07 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the crude mixture was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide as an off white solid.

Synthesis of 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

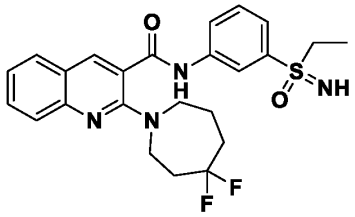
To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)quinoline-3-carboxamide (0.06 g, 0.07 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate and washed with saturated solution of sodium bicarbonate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford 8-chloro-2-(4,4-difluoro-3-methylpiperidin-1-yl)-*N*-(2-

sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a white solid. Yield: 0.009 g, 24%; LRMS (ESI): Calcd $[M+H]^+$: 496.10 found: 496.20.

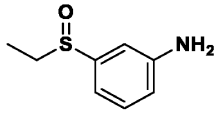
[00783] ^1H NMR (400 MHz, DMSO-d_6): δ 11.33 (br s, 1H), 8.64 (d, J = 5.2 Hz, 1H), 8.54 (s, 1H), 8.34 (d, J = 1.6 Hz, 1H), 7.90-7.85 (m, 3H), 7.48 (br s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 4.03-3.90 (m, 1H), 8.07-8.03 (m, 2H), 3.31-3.11 (m, 1H), 3.08-3.05 (m, 1H), 2.32-2.19 (m, 2H), 2.05-1.94 (m, 1H), 0.83 (d, J = 6.8 Hz, 3H).

Compound 104

Synthesis of (2-(4,4-difluoroazepan-1-yl)-N-(3-(ethylsulfonimidoyl)phenyl)quinoline-3-carboxamide

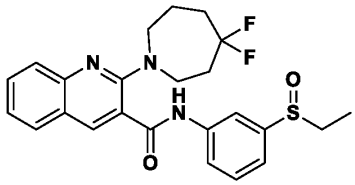


Synthesis of 3-(ethylsulfinyl)aniline



[00784] To a stirred suspension of 3-(ethylthio)aniline (0.2 g, 1.3 mmol) in water (4 mL) 30% w/w hydrogen peroxide (0.16 g, 1.4 mmol) was added at room temperature and the reaction mixture was heated at 70 °C for 2 hours. After reaction completion, the reaction mixture was quenched with saturated aqueous solution of sodium thiosulfate and extracted with dichloromethane. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated to afford 3-(ethylsulfinyl)aniline as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(ethylsulfinyl)phenyl)quinoline-3-carboxamide



[00785] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxylic acid (1 g, 3.3 mmol) in dichloromethane (40 mL), HATU (1.9 g, 5 mmol) and *N,N*-diisopropylethylamine (2.8 mL, 16.3 mmol) were added at 0-5 °C. After stirring for 5 min, a

solution of 3-(ethylsulfinyl)aniline (0.55 g, 3.26 mmol) was added at ambient temperature and the reaction mixture was heated at 80 °C for 6 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(ethylsulfinyl)phenyl)quinoline-3-carboxamide as a white solid.

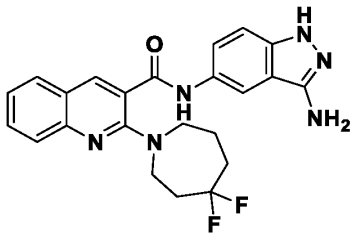
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-(ethylsulfonimidoyl)phenyl)quinoline-3-carboxamide

[00786] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(ethylsulfinyl)phenyl)quinoline-3-carboxamide (0.2 g, 0.44 mmol) in Eaton's reagent (5 mL), sodium azide (0.57 g, 0.87 mmol) was added at 0-5 °C. After complete addition of sodium azide, the reaction mixture was warmed to room temperature and then heated to 50 °C for 2 hours. After reaction completion, the reaction mixture was poured over crushed ice, neutralized with saturated aqueous solution of sodium carbonate, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-(ethylsulfonimidoyl)phenyl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.045 g, 22%; LRMS (ESI): Calcd $[M+H]^+$: 473.18 found: 473.20.

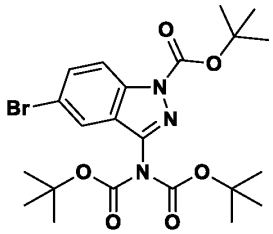
[00787] ^{1}H NMR (400 MHz, DMSO-d_6): 10.96 (s, 1H), 8.35 (s, 1H), 8.31 (s, 1H), 8.00-7.97 (m, 1H), 7.84 (d, J = 8 Hz, 1H), 7.64-7.58 (m, 4H), 7.32-7.28 (m, 1H), 4.18 (s, 1H), 3.76-3.73 (m, 2H), 3.60 (t, J = 8.0 Hz, 2H), 3.13 (q, J = 7.2 Hz, 2H), 2.45-2.37 (m, 2H), 2.01-1.96 (m, 2H), 1.89-1.88 (m, 2H), 1.09 (t, J = 7.6 Hz, 3H).

Compound 105

Synthesis of N-(3-amino-1H-indazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

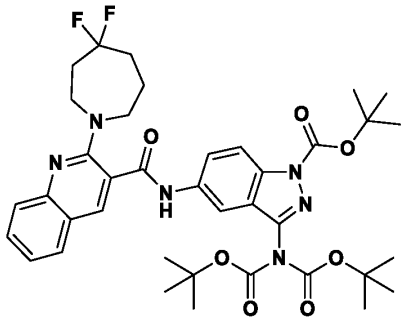


Synthesis of tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-5-bromo-1H-indazole-1-carboxylate



[00788] To a stirred solution of 5-bromo-1*H*-indazol-3-amine (0.2 g, 0.94 mmol), in tetrahydrofuran (10 mL) was added di-*tert*-butyl decarbonate (1. g, 4.7 mmol), *N,N*-diisopropylethylamine (1.2 g, 9.4 mmol) and DMAP (0.057 g, 0.047 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 3 hours. After reaction completion, the reaction mixture was diluted with water and extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-12% ethyl acetate in hexane to afford *tert*-butyl 3-(bis(*tert*-butoxycarbonyl)amino)-5-bromo-1*H*-indazole-1-carboxylate as a white solid.

Synthesis of tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-1H-indazole-1-carboxylate



[00789] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.1 g, 0.33 mmol) in 1,4-dioxane (5 mL), caesium carbonate (0.214 g, 0.66 mmol), BrettPhos Pd G3 (0.03 g, 0.033 mmol) and *tert*-butyl 3-(bis(*tert*-butoxycarbonyl)amino)-5-bromo-1*H*-indazole-1-carboxylate (0.17 g, 0.33 mmol) were added at 0-5 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and then heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium

sulfate, filtered, then concentrated to afford tert-butyl 3-(bis(*tert*-butoxycarbonyl)amino)-5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-1*H*-indazole-1-carboxylate as a white solid.

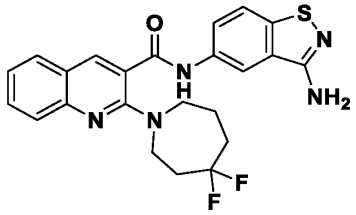
Synthesis of N-(3-amino-1H-indazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

[00790] To a stirred solution of *tert*-butyl 3-(bis(*tert*-butoxycarbonyl)amino)-5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-1*H*-indazole-1-carboxylate (0.15 g, 0.2 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.5 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with aqueous solution of sodium bicarbonate, extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by preparative HPLC to afford *N*-(3-amino-1H-indazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.010 g, 11%; LRMS (ESI): Calcd $[M+H]^+$: 437.19 found: 437.30.

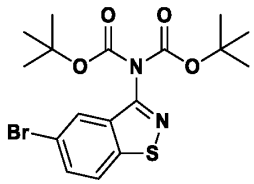
[00791] ^{1}H NMR (400 MHz, DMSO-d_6): 11.35 (s, 1H), 10.52 (s, 1H), 8.26 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.64-7.59 (m, 2H), 7.40-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 3.79-3.76 (m, 2H), 3.67 (t, J = 6.0 Hz, 2H), 2.44-2.41 (m, 2H), 2.05-1.97 (m, 2H), 1.91-1.89 (m, 2H).

Compound 106

Synthesis of N-(3-aminobenzo[d]isothiazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

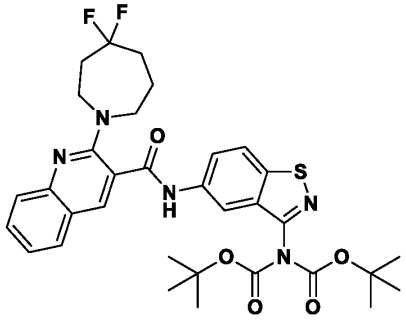


Synthesis of tert-butyl (5-bromobenzo[d]isothiazol-3-yl)(tert-butoxycarbonyl)carbamate



[00792] To a stirred solution of 5-bromobenzo[*d*]isothiazol-3-amine (0.3 g, 1.3 mmol) in anhydrous tetrahydrofuran (5 mL) was added di-*tert*-butyl dicarbonate (0.57 g, 2.6 mmol), *N,N*-diisopropylethylamine (0.85 g, 6.55 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP) (0.08 g, 0.66 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 3 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-12% ethyl acetate in hexane to afford *tert*-butyl (5-bromobenzo[*d*]isothiazol-3-yl)(*tert*-butoxycarbonyl)carbamate as a white solid.

Synthesis of tert-butyl (tert-butoxycarbonyl)(5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[d]isothiazol-3-yl)carbamate



[00793] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.2 g, 0.66 mmol) in 1,4-dioxane (10 mL), *tert*-butyl (5-bromobenzo[*d*]isothiazol-3-yl)(*tert*-butoxycarbonyl)carbamate (0.28 g, 0.66 mmol), BrettPhos Pd G3 (0.059 g, 0.067 mmol) and cesium carbonate (0.43 g) were added at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated to afford *tert*-butyl (*tert*-butoxycarbonyl) (5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[d]isothiazol-3-yl)carbamate as a white solid.

Synthesis of N-(3-aminobenzo[d]isothiazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide

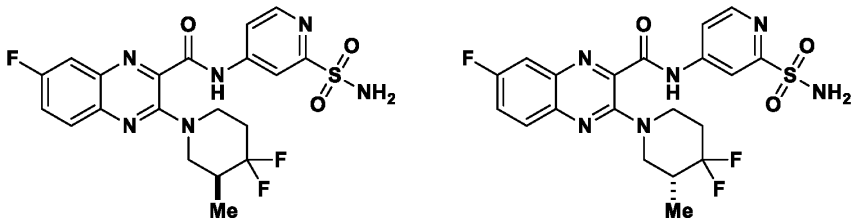
[00794] To a stirred solution of *tert*-butyl (*tert*-butoxycarbonyl)(5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)benzo[*d*]isothiazol-3-yl)carbamate (0.3 g, 0.46 mmol) in dichloromethane (10 mL), trifluoroacetic acid (1 mL) was added dropwise at 0-5 °C. The

reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with aqueous solution of sodium bicarbonate, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(3-aminobenzo[*d*]isothiazol-5-yl)-2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.088 g, 36%; LRMS (ESI): Calcd $[M+H]^+$: 454.15 found: 454.20.

[00795] ^{1}H NMR (400 MHz, DMSO-d_6): 10.83 (s, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.31 (s, 1H), 7.90 (d, J=8.8 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.66-7.60 (m, 3H), 7.33-7.29 (m, 1H), 6.74 (s, 2H), 3.79-3.76 (m, 2H), 3.66 (t, J = 6.0 Hz, 2H), 2.42-2.38 (m, 2H), 2.07-1.97 (m, 2H), 1.91-1.89 (m, 2H).

Compound 107 and 108

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide



[00796] To a stirred solution of*N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoxaline-2-carboxamide (0.20 g, 0.26 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the excess trifluoroacetic acid was distilled out. The residue was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated in vacuo to afford the residue which was purified through reversed phase prep-HPLC followed by Chiral SFC to afford 3-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide as off-white solids.

[00797] Peak-1: Yield: 0.037 g, 30%; LRMS (ESI): Calcd $[M+H]^+$: 481.13 found: 481.15.

[00798] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 8.68 (d, J = 5.2 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.93-7.91 (m, 1H), 7.88-7.80 (m, 2H), 7.75-7.70 (m, 1H), 7.50 (s, 2H),

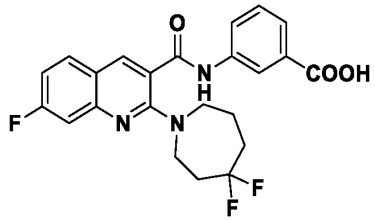
3.98-3.87 (m, 2H), 3.56-3.31 (m, 1H), 3.13-3.10 (m, 1H), 2.15-2.23 (m, 2H), 2.02-1.95 (m, 1H), 0.96-0.94 (d, J = 6.80 Hz, 3H).

[00799] Peak-2: Yield: 0.033 g, 26%; LRMS (ESI): Calcd $[M+H]^+$: 481.13 found: 481.20.

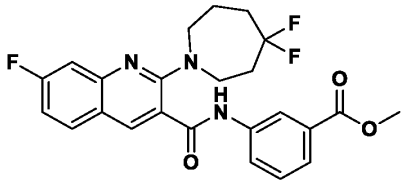
[00800] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 8.68 (d, J = 5.6 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 7.93-7.91 (m, 1H), 7.88-7.80 (m, 2H), 7.75-7.70 (m, 1H), 7.50 (s, 2H), 3.98-3.87 (m, 2H), 3.34-3.33 (m, 1H), 3.10 (t, J = 10.4 Hz, 1H), 2.24-2.21 (m, 2H), 2.01-1.95 (m, 1H), 0.95 (d J = 6.8 Hz, 3H).

Compound 109

Synthesis of 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoic acid



Synthesis of methyl 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoate



[00801] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.30 g, 0.92 mmol) in dichloromethane (5 mL) was added HATU (0.52 g, 1.4 mmol), *N,N*-dimethylpyridin-4-amine (0.006 g, 0.05 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo. To the reaction mixture was added a solution of methyl 3-aminobenzoate (0.16 g, 1.1 mmol) in acetonitrile (5 mL). The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo, water was added and extracted the compound with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoate as a white solid.

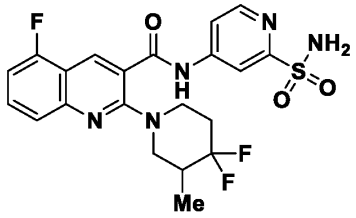
Synthesis of 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoic acid

[00802] To a solution of 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoate (0.18 g, 0.4 mmol) in methanol (3 mL), tetrahydrofuran (3 mL) and water (3 mL) was added lithium hydroxide monohydrate (0.038 g, 1.6 mmol). The mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and residue was acidified with 1*N* hydrochloric acid then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford 3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)benzoic acid as white a solid. Yield: 0.037 g, 21%; LRMS (ESI): Calcd $[M+H]^+$: 444.15 found: 444.20.

[00803] ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 10.84 (s, 1H), 8.37-8.36 (m, 2H), 7.95-7.90 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.32 (dd, J = 2.8, 11.2 Hz, 1H), 7.23-7.18 (m, 1H), 3.77-3.74 (m, 2H), 3.61 (t, J = 5.6 Hz, 2H), 2.50-2.49 (m, 2H), 2.01-1.96 (m, 2H), 1.90-1.88 (m, 2H).

Compound 110

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide



Synthesis of 2-amino-6-fluoro-N-methoxy-N-methylbenzamide



[00804] To a stirred solution of 2-amino-6-fluorobenzoic acid (2.5 g, 16 mmol) in *N,N*-dimethylformamide (10 mL), *N,O*-dimethylhydroxylamine (1.18 g, 19 mmol), HATU (9.2 g, 24.2 mmol) and *N,N*-Diisopropylethylamine (10.4 g, 80.6 mmol) were added at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, water was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash

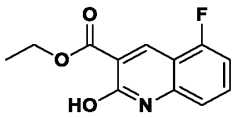
column chromatography with a gradient of 50-60% ethyl acetate in hexane to afford 2-amino-6-fluoro-*N*-methoxy-*N*-methylbenzamide as a white solid.

Synthesis of 2-amino-6-fluorobenzaldehyde



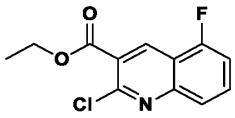
[00805] To a stirred solution of 2-amino-6-fluoro-*N*-methoxy-*N*-methylbenzamide (1.8 g, 9.1 mmol) in tetrahydrofuran (40 mL), lithium aluminum hydride (1.38 g, 36.3 mmol) was added at -78 °C. The reaction mixture was warmed to 20 °C over 6 hours. After reaction completion, the reaction was quenched with aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 15-20% ethyl acetate in hexane to afford 2-amino-6-fluorobenzaldehyde as a yellow solid.

Synthesis of ethyl 5-fluoro-2-hydroxyquinoline-3-carboxylate



[00806] To a stirred solution of 2-amino-6-fluorobenzaldehyde (1 g, 7.2 mmol) in ethanol (10 mL), diethyl malonate (2.3 g, 14.4 mmol) and piperidine (0.12 g, 1.44 mmol) were added at room temperature. The reaction mixture was heated at 70 °C for 20 hours. After reaction completion, water was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was triturated using acetonitrile to afford ethyl 5-fluoro-2-hydroxyquinoline-3-carboxylate as a white solid.

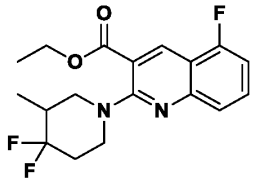
Synthesis of ethyl 2-chloro-5-fluoroquinoline-3-carboxylate



[00807] Phosphoryl chloride (10 mL) was added dropwise to a round bottom flask containing ethyl 5-fluoro-2-hydroxyquinoline-3-carboxylate (1.0 g, 4.25 mmol) at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 110 °C for 12 hours. After reaction completion, the reaction mixture was cooled to room temperature, poured over

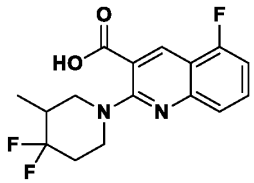
crushed ice and neutralized with saturated aqueous solution of sodium bicarbonate. The organic compounds were extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford ethyl 2-chloro-5-fluoroquinoline-3-carboxylate as an off white solid.

Synthesis of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylate



[00808] To a stirred solution of ethyl 2-chloro-5-fluoroquinoline-3-carboxylate (0.4 g, 1.6 mmol) in *N.N*-dimethylformamide (8 mL), 4,4-difluoro-3-methylpiperidine hydrochloride (0.32 g, 2.4 mmol) and potassium carbonate (0.87 g, 6.3 mmol) were added at room temperature. The reaction mixture was heated at 110 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylate as a white solid.

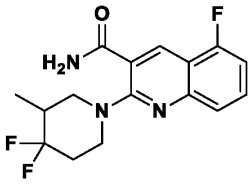
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylic acid



[00809] To a stirred solution of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylate (0.4 g, 1.14 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) a solution of lithium hydroxide (0.19 g, 4.7 mmol) in water (10 mL) was added. The reaction mixture was heated at 50 °C for 24 hours. After reaction completion, organic solvents were removed under reduced pressure and the resulting aqueous solution was neutralized with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was triturated

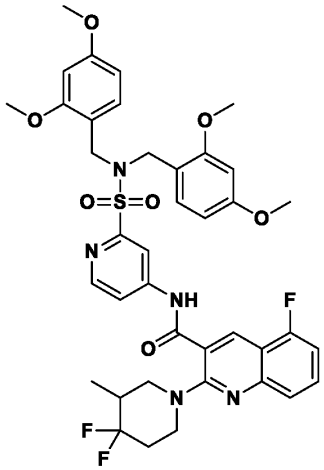
using pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide



[00810] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxylic acid (0.35 g, 1.1 mmol) in dichloromethane (50 mL), HATU (0.62 g, 1.6 mmol) and ammonium carbonate (1 g, 10.8 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, water was added and the mixture was extracted with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide



[00811] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide (0.1 g, 0.31 mmol) in 1,4-dioxane (5 mL), cesium carbonate (0.2 g, 0.62 mmol), BrettPhos Pd G3 (0.028 g, 0.030 mmol) and 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.17 g, 0.31 mmol) were added at 0-5 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and heated at 100 °C for 16 hours. After

reaction completion, the reaction mixture was cooled to room temperature, water was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide as a light yellow solid.

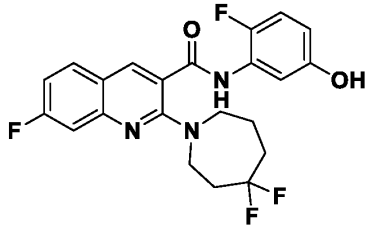
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00812] To a stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoroquinoline-3-carboxamide (0.2 g, 0.256 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.4 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.077 g, 63%; LRMS (ESI): Calcd $[M+H]^+$: 480.13 found: 480.20.

[00813] ^{1}H NMR (400 MHz, DMSO-d_6): 11.33 (s, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.52 (s, 1H), 8.35 (d, J = 1.6 Hz, 1H), 7.88 (dd, J = 5.2, 2.0 Hz, 1H), 7.70 (q, J = 8.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.48 (s, 2), 7.22 (t, J = 9.2 Hz, 1H), 3.94-3.84 (m, 2H), 3.31-3.22 (m, 1H), 3.05-2.99 (m, 1H), 2.21-2.15 (m, 2H), 2.03-1.92 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H).

Compound 111

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-fluoro-5-hydroxyphenyl)quinoline-3-carboxamide



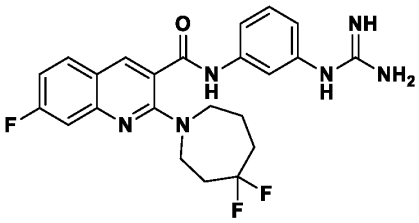
[00814] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.40 g, 1.2 mmol) in dichloromethane (5 mL) was added HATU (0.70 g, 1.8 mmol), *N*,*N*-dimethylpyridin-4-amine (0.008 g, 0.06 mmol) at 0 °C. The reaction mixture was stirred at

room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo. To the reaction mixture, a solution of 3-amino-4-fluorophenol (0.18 g, 1.4 mmol) in acetonitrile (5 mL) was added at room temperature. The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo, water was added and extracted the compound with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 25-30% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(2-fluoro-5-hydroxyphenyl)quinoline-3-carboxamide as a white solid. Yield: 0.10 g, 19%; LRMS (ESI): Calcd $[M+H]^+$: 434.15 found: 434.15.

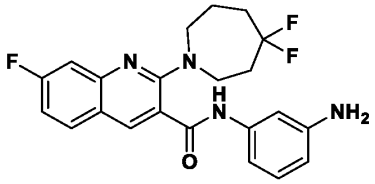
[00815] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 9.49 (s, 1H), 8.31 (s, 1H), 7.95-7.91 (m, 1H), 7.47-7.30 (m, 2H), 7.21-7.17 (m, 1H), 7.08 (t, J = 10.0 Hz, 1H), 6.59-6.55 (m, 1H), 3.76-3.75 (m, 2H), 3.63 (t, J = 5.6 Hz, 2H), 2.44-2.40 (m, 2H), 2.04-1.98 (m, 2H), 1.92-1.90 (m, 2H).

Compound 112

Synthesis of 1-(3-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)phenyl)guanidinium



Synthesis of N-(3-aminophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



[00816] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.20 g, 0.61 mmol) in dichloromethane (6 mL) was added oxalylchloride (0.1 mL, 1.2 mmol) and 2 drops of *N,N*-dimethylformamide (DMF) at 0 °C and stirred the reaction for 2 hours at room temperature. After reaction completion, solvent was removed under nitrogen atmosphere.

The crude was dissolved into dry dichloromethane (6 mL) and added to the solution of benzene-1,3-diamine (0.18 mg, 0.73 mmol) and DIPEA (0.4 mL, 3.5 mmol) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for additional 12 hours at room temperature. After reaction completion, the mixture was quenched with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to afford residue which was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(3-aminophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a light brown solid.

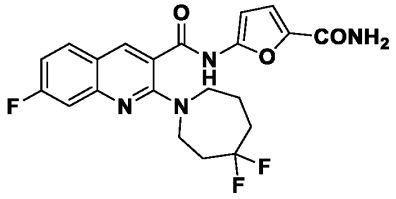
Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(3-guanidinophenyl)quinoline-3-carboxamide

[00817] To a solution of *N*-(3-aminophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.10 g, 0.24 mmol) in 4M hydrochloric acid in dioxane (2 mL) was added cyanamide (50 mg, 1.2 mmol). The reaction mixture was heated at 60 °C for 16 hours. After reaction completion, the solvent was removed in vacuo and purified by prep HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(3-guanidinophenyl) quinoline-3-carboxamide as yellow solid. Yield: 0.025 g, 23%; LRMS (ESI): Calcd $[M+H]^+$: 457.20 found: 457.25.

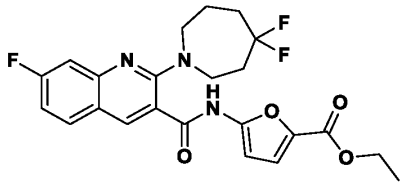
[00818] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H), 9.72 (s, 1H), 8.30 (s, 1H), 7.94-7.90 (m, 1H), 7.74 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.45-7.41 (m, 4H), 7.32 (dd, J = 11.2, 2.4 Hz, 1H), 7.21 (dt, J = 8.8, 2.4 Hz, 1H), 6.97 (d, J = 16.8 Hz, 1H), 3.81-3.74 (m, 2H), 3.61 (t, 2H), 2.39-2.37 (m, 2H), 2.00-1.96 (m, 2H), 1.89-1.88 (m, 2H).

Compound 113

Synthesis of N-(5-carbamoylfuran-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

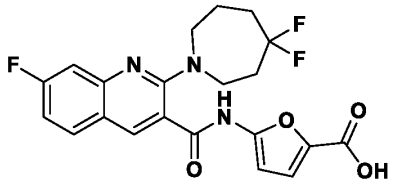


Synthesis of ethyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylate



[00819] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.30 g, 0.92 mmol) in 1,4-dioxane (3 mL) was added ethyl 5-bromofuran-2-carboxylate (0.19 g, 1.1 mmol), cesium carbonate (0.59 g, 1.8 mmol) consecutively under nitrogen atmosphere. After degassing for 10 min, BrettPhos Pd G3 (0.08 g, 0.09 mmol) was added and slowly heated the mixture at 120 °C for 12 hours. After reaction completion, the solvent was removed in vacuo, brine was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford ethyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylate as a white solid.

Synthesis of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylic acid



[00820] To a solution of ethyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylate (0.15 g, 0.34 mmol) in methanol (3 mL), tetrahydrofuran (3 mL) and water (3 mL) was added lithium hydroxide (0.07 g, 1.4 mmol). The mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and acidified with hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylic acid as a white solid.

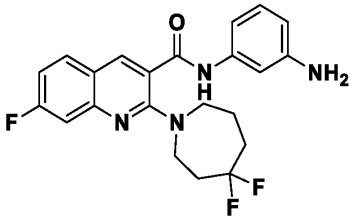
Synthesis of N-(5-carbamoylfuran-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00821] To a solution of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)furan-2-carboxylic acid (0.09 g, 0.21 mmol) in *N,N*-dimethylformamide (4 mL) was added HATU (0.12 g, 0.31 mmol), *N,N*-diisopropylethylamine (0.2 mL, 1.0 mmol) and ammonium chloride (0.11 g, 2.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(5-carbamoylfuran-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.013 g, 15%; LRMS (ESI): Calcd $[M+H]^+$: 433.15 found: 433.15.

[00822] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.93 (br s, 1H), 8.35 (s, 1H), 7.91-7.87 (m, 1H), 7.55 (br s, 1H), 7.31 (dd, J = 2.4, 11.2 Hz, 1H), 7.22-7.17 (m, 3H), 6.45 (d, J = 3.6 Hz, 1H), 3.73-3.70 (m, 2H), 3.52 (t, J = 5.6 Hz, 2H), 2.44-2.36 (m, 2H), 2.07-1.94 (m, 2H), 1.90-1.75 (m, 2H).

Compound 114

Synthesis of N-(3-aminophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



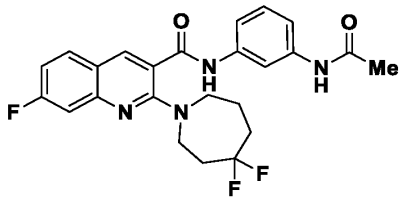
[00823] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.2 g, 0.7 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.12 mL, 1.4 mmol) under nitrogen atmosphere followed by the addition of 2 drops of *N,N*-dimethylformamide at 0 °C and the mixture was stirred for 2 hour at room temperature. After reaction completion, the solvent was removed under nitrogen atmosphere. The reaction mixture was dissolved into dichloromethane (6 mL) and added to a solution of benzene-1,3-diamine (0.09 g, 0.84 mmol) and *N,N*-diisopropylethylamine (0.6 mL, 3.5 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred for additional 12 hours at room temperature. After reaction

completion, the reaction mixture was quenched with water, extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford *N*-(3-aminophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.018 g, 7%; LRMS (ESI): Calcd $[M+H]^+$: 415.17 found: 415.25.

[00824] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.25 (s, 1H), 7.93-7.89 (m, 1H), 7.30 (dd, J = 2.4, 11.2 Hz, 1H), 7.20-7.15 (m, 1H), 7.05-7.04 (m, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 5.12 (s, 2H), 3.76-3.74 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.42-2.35 (m, 2H), 2.02-1.99 (m, 2H), 1.89-1.88 (m, 2H).

Compound 115

Synthesis of N-(3-acetamidophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

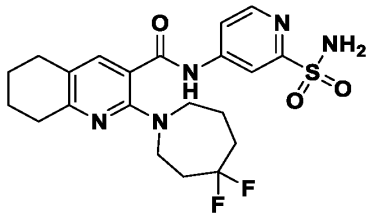


[00825] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.2 g, 0.62 mmol) in dichloromethane (4 mL) was added HATU (0.35 g, 0.92 mmol), *N,N*-dimethylpyridin-4-amine (0.002 g, 0.02 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo. To the reaction mixture was added a solution of *N*-(3-aminophenyl)acetamide (0.11 g, 0.74 mmol) in acetonitrile (4 mL). The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the solvent was removed in vacuo, water was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC to afford *N*-(3-acetamidophenyl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.03 g, 11%; LRMS (ESI): Calcd $[M+H]^+$: 457.18 found: 457.10.

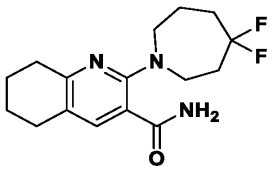
[00826] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 9.98 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.93-7.89 (m, 1H), 7.38-7.17 (m, 5H), 3.75-3.74 (m, 2H), 3.62 (t, J = 5.6 Hz, 2H), 2.49-2.38 (m, 2H), 2.07 (s, 3H), 1.99-1.96 (m, 2H), 1.89-1.88 (m, 2H).

Compound 116

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

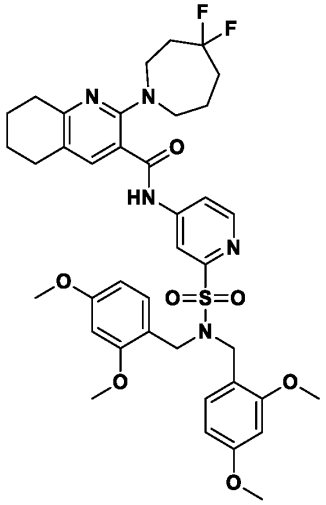


Synthesis of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00827] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylic acid (0.5 g, 1.6 mmol) in *N*,*N*-dimethylformamide (5 mL) was added HATU (0.92 g, 2.4 mmol), *N*,*N*-diisopropylethylamine (1.4 mL, 8 mmol) and ammonium chloride (0.42 g, 16 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



[00828] To a solution of 2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.45 g, 1.5 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.93 g, 1.7 mmol), cesium carbonate (0.97 g, 3.0 mmol) and BrettPhos Pd G3 (0.12 g, 0.15 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid.

Synthesis of2-(4,4-difluoroazepan-1-yl)-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide

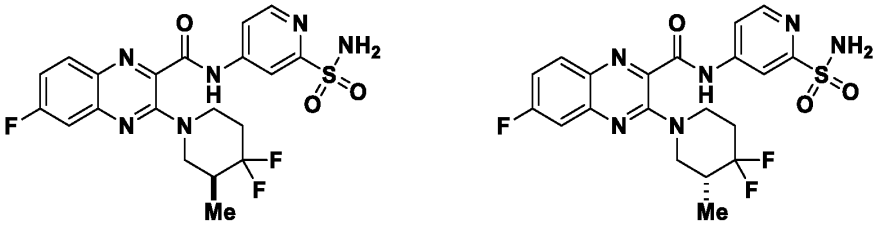
[00829] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.14 g, 0.18 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.7 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the solvent was removed in vacuo and the residue was dissolved into ethyl acetate and washed with saturated solution of sodium bicarbonate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through

reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as a white solid. Yield: 0.03 g, 35%; LRMS (ESI): Calcd $[M+H]^+$: 466.17 found: 466.15.

[00830] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.57 (d, J = 5.2 Hz, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.82-7.80 (m, 1H), 7.48 (s, 1H), 7.42 (brs, 2H), 3.57-3.55 (m, 2H), 3.34-3.32 (m, 2H), 2.70-2.62 (m, 4H), 2.33-2.26 (m, 2H), 1.95-1.89 (m, 2H), 1.80-1.75 (m, 4H), 1.73-1.71 (m, 2H).

Compound 117 and 118

Synthesis of 3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide



[00831] To a stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoxaline-2-carboxamide (0.2 g, 0.26 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the excess trifluoroacetic acid was distilled out. The residue was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase prep-HPLC followed by Chiral SFC to afford S and R-3-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoxaline-2-carboxamide as an off-white solids.

[00832] Peak-1: Yield: 0.040 g, 32.5%; LRMS (ESI): Calcd $[M+H]^+$: 481.13 found: 481.4.

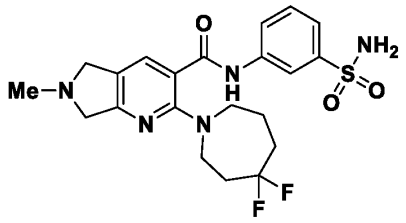
[00833] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.67 (d, J = 5.6 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.08-8.05 (m, 1H), 7.95-7.93 (m, 1H), 7.56-7.48 (m, 4H), 4.03-3.92 (m, 2H), 3.36-3.31 (m, 1H), 3.16-3.10 (m, 1H), 2.32-2.19 (m, 2H), 2.04-1.96 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H).

[00834] Peak-2: Yield: 0.036 g, 29%; LRMS (ESI): Calcd $[M+H]^+$: 481.13 found: 481.4.

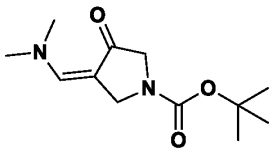
[00835] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (br s, 1H), 8.63 (d, J = 6.5 Hz, 1H), 8.37 (br s, 1H), 8.07-8.03 (m, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.54-7.47 (m, 4H), 4.06-3.95 (m, 2H), 3.36-3.31 (m,1H), 3.13 (t, J = 10.0 Hz, 1H), 2.32-2.19 (m, 2H), 2.10-1.98 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H).

Compound 119

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide

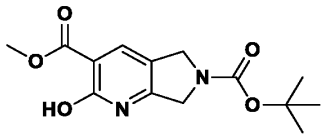


Synthesis of tert-butyl (Z)-3-((dimethylamino)methylene)-4-oxopyrrolidine-1-carboxylate



[00836] To a stirred solution of *tert*-butyl 3-oxopyrrolidine-1-carboxylate (10 g, 54 mmol) in tetrahydrofuran (100 ml) was added 1,1-dimethoxy-*N,N*-dimethylmethanamine (19.3 g, 162 mmol) and refluxed the reaction mixture at 100 °C for 5 hours. After reaction completion, the solvent was removed in vacuo and the residue was triturated with hexane to afford *tert*-butyl (*Z*)-3-((dimethylamino)methylene)-4-oxopyrrolidine-1-carboxylate as a brown solid.

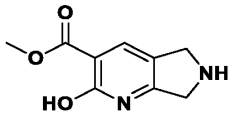
Synthesis of 6-(tert-butyl) 3-methyl 2-hydroxy-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-3,6-dicarboxylate



[00837] To a stirred solution of *tert*-butyl (*Z*)-3-((dimethylamino)methylene)-4-oxopyrrolidine-1-carboxylate (12 g, 50 mmol) in methanol (60 mL) was added methyl 2-cyanoacetate (10 mL, 100 mmol) and the reaction mixture was heated at 80 °C for 24 hours. After reaction completion, methanol was removed under reduced pressure and the residue was purified by flash chromatography with a gradient of 5-8% methanol in dichloromethane to

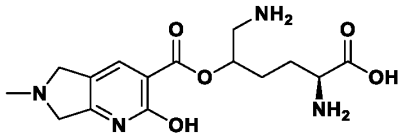
afford 6-(*tert*-butyl) 3-methyl 2-hydroxy-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-3,6-dicarboxylate as a brown solid.

Synthesis of methyl 2-hydroxy-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylate



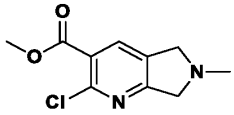
[00838] 6-(*tert*-butyl) 3-methyl 2-hydroxy-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-3,6-dicarboxylate (7.0 g, 23 mmol) was dissolved into 4M hydrochloric acid in 1,4-dioxane (70 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After the completion of reaction, the reaction mixture was concentrated. The residue was triturated with diethyl ether and pentane to afford methyl 2-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate as a light brown solid.

Synthesis methyl 2-hydroxy-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylate



[00839] To a solution of methyl 2-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylatein methanol (80 mL) and dichloromethane (40 mL) was added formaldehyde (2.32 mL, 62 mmol) and acetic acid (2.5 mL, 41.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After reaction completion, sodium triacetoxy-borohydride (6.6 g, 31 mmol) was added 0 °C and stirred at room temperature for 18 hours. After reaction completion, the reaction mixture was quenched with aqueous sodium bicarbonate solution and extracted with 10% methanol in dichloromethane. The organic layers were combined, dried by sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford methyl 2-hydroxy-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate as an off-white solid.

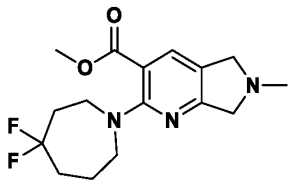
Synthesis of methyl 2-chloro-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylate



[00840] To a solution of methyl 2-hydroxy-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate (2.0 g, 9.6 mmol) in acetonitrile (20 ml) was added phosphoryl

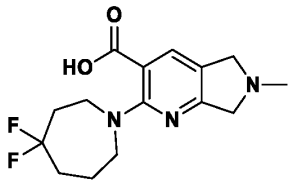
trichloride (1.8 mL, 19.2 mmol) at room temperature and refluxed the reaction mixture at 110 °C for 12 hours. After reaction completion, the reaction mixture was quenched with aqueous solution of sodium carbonate and extracted with 10% methanol in dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, then concentrated to afford methyl 2-chloro-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate as a brown solid which was used directly into next step without purification.

Synthesis of methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylate



[00841] To a solution of methyl 2-chloro-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate (2.0 g, 8.8 mmol) in *N,N*-dimethylformamide (20 mL) was added potassium carbonate (4.9 g, 35.3 mmol) and 4,4-difluoroazepane hydrochloride (2.3 g, 13.2 mmol) at room temperature. The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was quenched by ice cold water and extracted with 10% methanol in dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by combi-flash chromatography with a gradient of 15-20% methanol in dichloromethane to afford methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate as a brown solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylic acid



[00842] To a solution of methyl 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylate (0.4 g, 1.2 mol) in methanol (10 mL) was added 2 M solution of sodium hydroxide (4 mL) at room temperature. The reaction mixture was refluxed at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated and the

residue was purified through reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylic acid as a white solid.

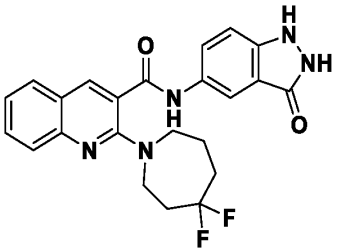
Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-methyl-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide

[00843] To a solution of 2-(4,4-difluoroazepan-1-yl)-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxylic acid (0.18 g, 0.60 mmol) in dichloromethane (5 mL) was added HATU (0.33 g, 0.90 mmol) and *N,N*-dimethylpyridin-4-amine (0.035 g, 0.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved into acetonitrile (5 mL) and 3-aminobenzene-1-sulfonamide (0.12 g, 0.72 mmol) was added at room temperature. The reaction mixture was refluxed at 80 °C for 16 hours. After reaction completion, the solvent was removed in vacuo and the reaction mixture was diluted with water, extracted with 10% methanol in dichloromethane. The organic layers were dried over sodium sulfate, filtered, then concentrated. The residue was purified through reversed phase pre-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-6-methyl-*N*-(3-sulfamoylphenyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide as a white solid. LRMS (ESI): Calcd $[M+H]^+$: 466.17 found: 466.4.

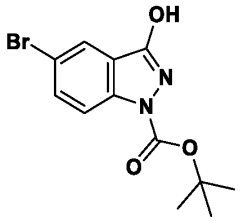
[00844] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.31-8.29 (t, J = 2 Hz, 1H), 7.81-7.78 (m, 1H), 7.61 (s, 1H), 7.54-7.49 (m, 2H), 7.39 (brs, 2H), 3.77 (s, 2H), 3.72 (s, 2H), 3.59-3.57 (m, 2H), 3.39 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.38-2.32 (m, 2H), 1.97-1.94 (m, 2H), 1.90-1.83 (m, 2H).

Compound 120

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-oxo-2,3-dihydro-1H-indazol-5-yl)quinoline-3-carboxamide

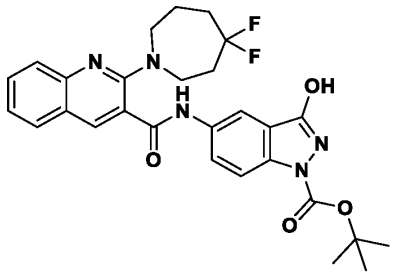


Synthesis of tert-butyl 5-bromo-3-hydroxy-1H-indazole-1-carboxylate



[00845] To a stirred solution of 5-bromo-1*H*-indazol-3-ol (0.5 g, 2.35 mmol) in tetrahydrofuran (5 mL), di-*tert*-butyl dicarbonate (1.0 g, 4.7 mmol), *N,N*-diisopropylethylamine (1.5 g, 11.7 mmol), *N,N*-dimethylpyridin-4-amine (0.14 g, 1.2 mmol) was added at 0-5 °C. The reaction mixture was stirred at room temperature for 3 hours. After reaction completion, water was added and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *tert*-butyl 5-bromo-3-hydroxy-*1H*-indazole-1-carboxylate as a white solid.

Synthesis of tert-butyl 5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-3-hydroxy-1H-indazole-1-carboxylate



[00846] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamide (0.2 g, 0.66 mmol) in 1,4-dioxane (5 mL), cesium carbonate (0.43 g, 1.3 mmol), BrettPhos Pd G3 (0.059 g, 0.65 mmol) and *tert*-butyl 5-bromo-3-hydroxy-1*H*-indazole-1-carboxylate (0.21 g, 0.66 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 100 °C for 24 hours. After reaction completion, water was added and extraction was performed with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated to afford *tert*-butyl 5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-3-hydroxy-1*H*-indazole-1-carboxylate as a white solid.

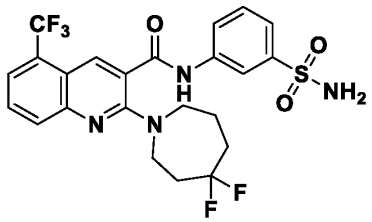
Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-hydroxy-1H-indazol-5-yl)quinoline-3-carboxamide

[00847] To a stirred solution of *tert*-butyl 5-(2-(4,4-difluoroazepan-1-yl)quinoline-3-carboxamido)-3-hydroxy-1*H*-indazole-1-carboxylate (0.1 g, 0.19 mmol) in dichloromethane (10 mL), trifluoroacetic acid (1 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous solution of sodium bicarbonate, extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-hydroxy-1*H*-indazol-5-yl)quinoline-3-carboxamidewas obtained as a pale yellow solid. Yield: 0.015 g, 18%; LRMS (ESI): Calcd $[M+H]^+$: 438.17 found: 438.25.

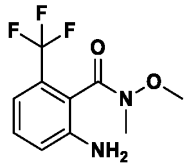
[00848] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (br s, 1H), 10.62 (s, 1H), 8.32 (s, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.64-7.61 (m, 2H), 7.50 (dd, J = 9.2, 2.0 Hz, 1H), 7.33-7.28 (m, 2H), 4.06 (br s, 1H), 3.75 (d, J =3.6 Hz, 2H), 3.66 (t, J = 6.0 Hz, 2H), 2.40-2.37 (m, 2H), 2.01-1.97 (m, 2H), 1.90-1.89 (m, 2H).

Compound 121

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)quinoline-3-carboxamide



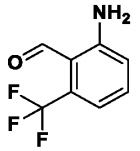
Synthesis of 2-amino-N-methoxy-N-methyl-6-(trifluoromethyl)benzamide



[00849] To a stirred solution of 2-amino-6-(trifluoromethyl)benzoic acid (3 g, 14.6 mmol) in *N,N*-dimethylformamide (30 mL), *N,O*-dimethylhydroxylamine hydrochloride (1.7 g, 17.5 mmol), HATU (8.3 g, 22 mmol) and *N,N*-diisopropylethylamine (9.45 g, 73 mmol) were added

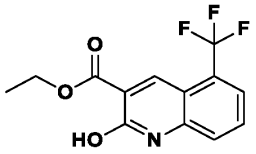
at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water and extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford 2-amino-*N*-methoxy-*N*-methyl-6-(trifluoromethyl)benzamide as a white solid.

Synthesis of 2-amino-6-(trifluoromethyl)benzaldehyde



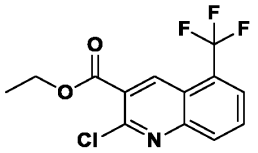
[00850] To a stirred solution of 2-amino-*N*-methoxy-*N*-methyl-6-(trifluoromethyl)benzamide (1.5 g, 6.0 mmol) in tetrahydrofuran (40 mL), lithium aluminum hydride (1.4 g, 36 mmol) was added at -78 °C. The reaction mixture was warmed to room temperature over 6 hours. After reaction completion, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 15-20% ethyl acetate in hexane to afford 2-amino-6-(trifluoromethyl)benzaldehyde as a white solid.

Synthesis of ethyl 2-hydroxy-5-(trifluoromethyl)quinoline-3-carboxylate



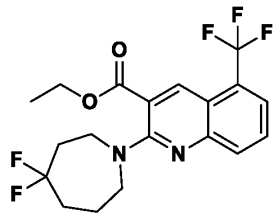
[00851] To a stirred solution of 2-amino-6-(trifluoromethyl)benzaldehyde (1.0 g, 5.3 mmol) in ethanol (20 mL), diethyl malonate (3.4 g, 21 mmol) and piperidine (0.225 g, 2.64 mmol) were added and the reaction mixture was heated at 70 °C for 20 hours. After reaction completion, the reaction mixture was diluted with water and extracted in ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with acetonitrile to afford ethyl 2-hydroxy-5-(trifluoromethyl)quinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-chloro-5-(trifluoromethyl)quinoline-3-carboxylate



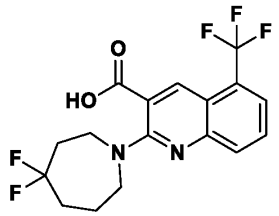
[00852] Phosphorus oxychloride (5 mL) was added dropwise to a round bottom flask containing ethyl 2-hydroxy-5-(trifluoromethyl)quinoline-3-carboxylate (0.5 g, 1.75 mmol) at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 110 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, poured over ice-cold water and neutralized with aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford ethyl 2-chloro-5-(trifluoromethyl)quinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylate



[00853] To a stirred solution of ethyl 2-chloro-5-(trifluoromethyl)quinoline-3-carboxylate (0.3 g, 1 mmol) in *N,N*-dimethylformamide (5 mL), 4,4-difluoroazepane hydrochloride(0.2 g, 1.2 mmol) and potassium carbonate (0.55 g, 4 mmol) were added. The reaction mixture was heated at 110 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-35% ethyl acetate in hexane to afford ethyl 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylic acid



[00854] To a stirred solution of ethyl 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylate (0.15 g, 0.37 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) a solution of lithium hydroxide (0.035 g, 0.74 mmol) in water (10 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, organic solvents were removed under reduced pressure and the resulting aqueous solution was neutralized with hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with pentane to afford 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)quinoline-3-carboxamide

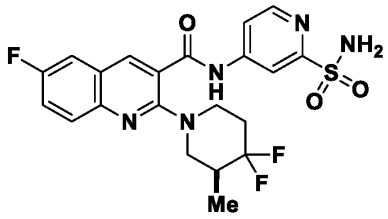
[00855] To a stirred suspension of 2-(4,4-difluoroazepan-1-yl)-5-(trifluoromethyl)quinoline-3-carboxylic acid (0.12 g, 0.32 mmol) in dichloromethane (5 mL), HATU (0.06 g, 0.16 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP) (0.02 g, 0.16 mmol) were added at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated to remove the dichloromethane under nitrogen atmosphere and the residue was dissolved in acetonitrile (5 mL). To the reaction mixture, 3-aminobenzene-1-sulfonamide (0.066 g, 0.38 mmol) was added and the reaction mixture was refluxed for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-*N*-(3-sulfamoylphenyl)-5-(trifluoromethyl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.07 g, 4%; LRMS (ESI): Calcd $[M+H]^+$: 529.13 found: 529.30.

[00856] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (br s, 1H), 8.29-8.28 (m, 1H), 8.24 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.89-7.85 (m, 1H), 7.80-7.73 (m, 2H), 7.61-7.56 (m, 2H), 7.42 (br s,

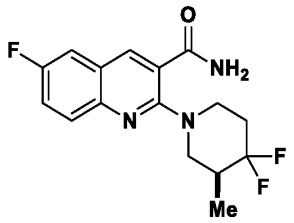
2H), 3.82-3.79 (m, 2H), 3.64 (t, J = 6.0 Hz, 2H), 2.47-2.41 (m, 2H), 2.08-1.98 (m, 2H), 1.92-1.90 (m, 2H).

Compound 122

Synthesis of (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

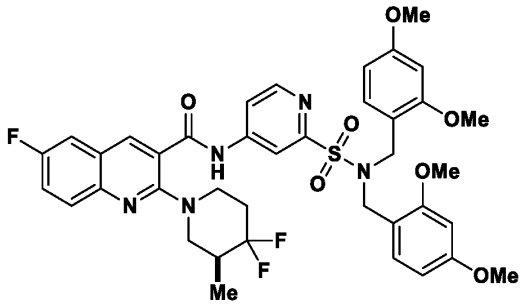


Synthesis of (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[00857] To a solution of 2-chloro-6-fluoroquinoline-3-carboxamide in *N,N*-dimethylformamide was added (*S*)-4,4-difluoro-3-methylpiperidin-1-yl and potassium carbonate. The mixture was heated at 80 °C for 18 hours under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion, the crude material was diluted with water and extracted with isopropyl acetate. The organic layers were separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel with a gradient of ethyl acetate in hexanes to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide.

Synthesis of (S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[00858] To a solution of (S)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide in 1,4-dioxane was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide, cesium carbonate, BrettPhos, and BrettPhos Pd G3. The atmosphere was replaced with nitrogen then the reaction mixture was heated at 120 °C for 12 hours. After reaction completion, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to afford *(S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide.*

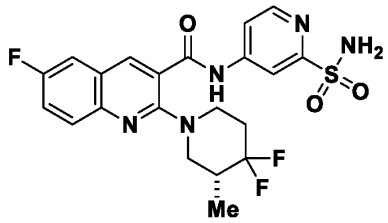
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00859] A round bottom flask was charged with (S)-N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide (29 g, 37.5 mmol) and DCM (376 mL). TFA (173 mL, 2.25 mol) was added slowly and the solution was stirred at room temperature for 18 hours. When the reaction was complete, TFA was removed in vacuo and the residue was taken up in DCM. The DCM solution was neutralized using saturated aqueous sodium bicarbonate. The organic layers were concentrated and the residue was diluted with ethyl acetate. The solution was filtered and the and hexanes were added to the filtrate. The precipitate was collected by vacuum filtration and the product was obtained as a yellow powder (17.3 g, 97%). LRMS (ESI): Calcd $[M+H]^+$: 480.13 found: 480.15.

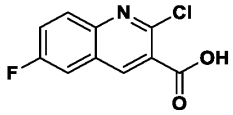
[00860] ^{1}H NMR (400 MHz, MeCN-d6): δ 8.64 (d, J = 5.2 Hz, 1H), 8.46 (s, 1H), 8.36 (d, J = 1.2 Hz, 1H), 7.84-7.79 (m, 2H), 7.47 (dd, J = 6.0 Hz, 2.8 Hz, 1H), 7.30-7.24 (m, 1H), 3.89-3.76 (m, 2H), 3.29 (t, J = 11.6 Hz, 1H), 3.02 (t, J = 10.8 Hz, 1H), 2.18-1.99 (m, 3H), 0.99 (d, J = 6.8 Hz, 3H).

Compound 123

Synthesis of (R)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

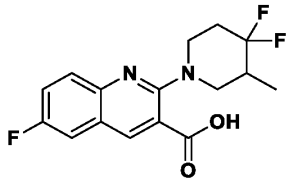


Synthesis of 2-chloro-6-fluoroquinoline-3-carboxylic acid



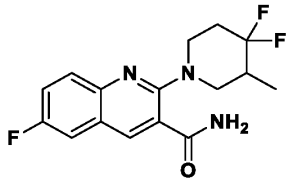
[00861] To a stirred solution of silver nitrate (0.78 g, 4.6 mmol) in water (10 ml) was added sodium hydroxide (0.57 g, 14.3 mmol) and the reaction mixture was stirred for 30 min at room temperature. A solution of 2-chloro-6-fluoroquinoline-3-carbaldehyde (0.6 g, 2.86 mmol) in ethanol (20 ml) was added dropwise to the reaction mixture and stirred at room temperature for 5 hours. After reaction completion, the reaction mixture was filtered through Celite, the solvent was removed in vacuo, diluted with water, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to afford 2-chloro-6-fluoroquinoline-3-carboxylic acid as a light yellow solid which was used directly into next step.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid



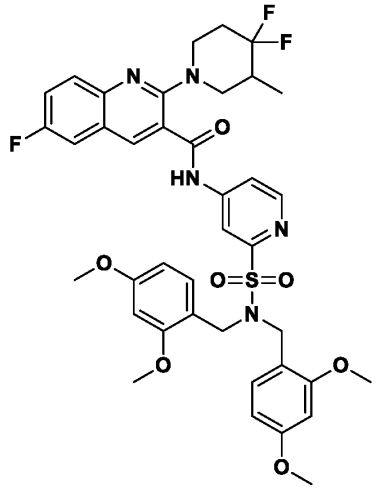
[00862] To a solution of 2-chloro-6-fluoroquinoline-3-carboxylic acid (0.45 g, 1.4 mmol) in *N,N*-dimethylformamide (5 ml) was added potassium carbonate (0.31 g, 2.25 mmol) and 4,4-difluoro-3-methylpiperidine hydrochloride (0.36 g, 2.1 mmol) at room temperature and the reaction mixture was heated at 80 °C for 16 hours. After reaction completion, the reaction mixture was quenched by ice cold water and acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was triturated with ether and pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[00863] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxylic acid (0.45 g, 1.4 mmol) in dichloromethane (9 mL) was added HATU (0.79 g, 2.1 mmol) and ammonium carbonate (1.3 g, 14 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 25-30% ethyl acetate in hexanes to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide as a yellow solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[00864] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide (0.33 g, 1 mmol) in 1,4-dioxane (6.6 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.66 g, 1.22 mmol) and cesium carbonate (1 g, 3.06 mmol) at room temperature and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.093 g, 0.102) was added and the reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was extracted with water and ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexanes to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide as a white solid.

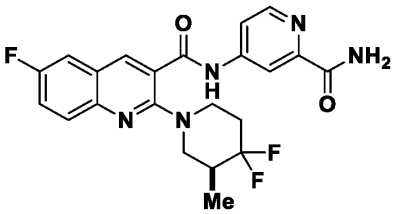
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

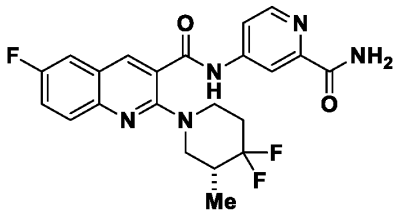
To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide (0.66 g, 0.85 mmol) in dichloromethane (6.6 mL) was added trifluoroacetic acid (3.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 hours. After reaction completion, the reaction mixture was concentrated, the residue was neutralized with saturated sodium bicarbonate solution, then extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to give 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide which was further purified by chiral SFC. Yield: 0.08 g, 20%; LRMS (ESI): Calcd $[M+H]^+$: 480.13 found: 480.15.

[00865] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 8.65 (d, J = 5.2 Hz, 1H), 8.49 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 7.86 (dd, J = 2.0, 3.6 Hz, 1H), 7.83-7.79 (m, 1H), 7.76 (dd, J = 2.8, 6.4 Hz, 1H), 7.65-7.60 (m, 1H), 7.51 (s, 2H), 3.86-3.76 (m, 2H), 3.21 (t, J = 11.6 Hz, 1H), 2.97 (t, J = 10.4 Hz, 1H), 2.17-2.14 (m, 2H), 2.01-1.88 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H).

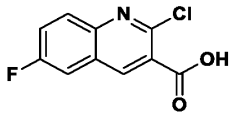
Compound 124 and 125

Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide (Peak-1 & Peak-2)





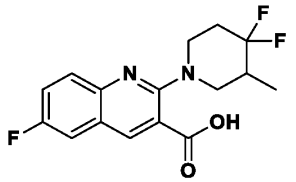
Synthesis of 2-chloro-6-fluoroquinoline-3-carboxylic acid



[00866] To a stirred solution of silver nitrate (6.5 g, 3.2 mmol) in water (15 mL) was added sodium hydroxide (4.8 g, 10.6 mmol) and the reaction mixture was stirred for 30 min at room temperature. A solution of 2-chloro-6-fluoroquinoline-3-carbaldehyde (5 g, 2.1 mmol) in ethanol (80 mL) was added dropwise to the reaction mixture and the reaction mixture was

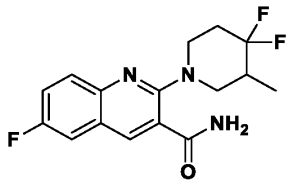
stirred at room temperature for 5 hours. After reaction completion reaction, the reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was diluted with water and acidified 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to afford 2-chloro-6-fluoroquinoline-3-carboxylic acid as a yellow solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid



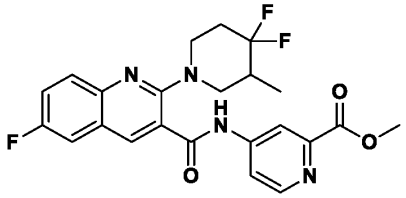
[00867] To a solution of 2-chloro-6-fluoroquinoline-3-carboxylic acid (1.0 g, 4.4 mmol) in *N,N*-dimethylformamide (7 mL) was added potassium carbonate (3.1 g, 22 mmol) and 4,4-difluoro-3-methylpiperidine hydrochloride (0.9 g, 6.7 mmol) and the reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was acidified with 1*N* hydrochloric acid and extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



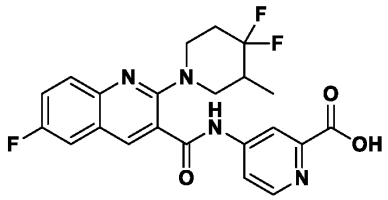
[00868] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid (0.9 g, 2.8 mmol) in *N,N*-dimethylformamide (15 mL) was added *N,N*-diisopropylethylamine (2.4 mL,14 mmol), HATU (0.98 g, 4.2 mmol) and ammonium chloride (1.5 g, 28 mmol) at 0 °C. The reaction mixture was stirred room temperature for 12 hours. After reaction completion, the reaction mixture was quenched by ice-cold water and extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide as a yellow solid.

Synthesis of methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinate



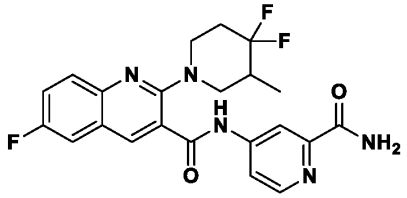
[00869] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide (0.4 g, 1 mmol) in 1,4-dioxane (10 mL) was added methyl 4-bromopyridine-2-carboxylate (0.32 g, 1.5 mmol) and cesium carbonate (0.97 g, 3 mmol) and the reaction mixture was degassed with nitrogen for 15 min. BrettPhos Pd G3 (0.089 mg) was added under nitrogen atmosphere and the reaction mixture was refluxed at 100 °C for 12 hours. After reaction completion, the reaction mixture was extracted by ethyl acetate and water. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexane to afford methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinate as a yellow solid.

Synthesis of 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinic acid



[00870] To a solution of methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinate (0.8 g, 1.7 mmol) in tetrahydrofuran (10 mL), methanol (10 mL) was added lithium hydroxide mono hydrate (0.21 g, 8.7 mmol) in water (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, reaction mixture was concentrated. The residue was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient 0-10% MeOH in dichloromethane to afford 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinic acid as a white solid.

Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[00871] To a solution of 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)picolinic acid (0.35 g 0.8 mmol) in *N,N*-dimethylformamide (10mL) was added *N,N*-diisopropylethylamine (0.68 mL, 3.9 mmol), HATU (0.45 g, 1.2 mmol) and ammonium carbonate (0.37 g, 3.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was quenched by ice cold water and extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient 20-25% ethyl acetate in hexane to afford *N*-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide as a yellow solid. Chiral SFC was used to separate the enantiomers, both of which were white solids.

[00872] Peak-1: Yield: 0.035 g, LRMS (ESI): Calcd $[M+H]^+$: 444.16 found: 444.4.

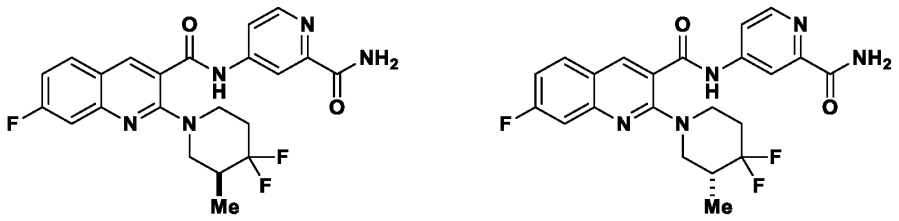
[00873] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (s, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.90-7.82 (m, 1H), 7.82-7.80 (m, 1H), 7.78-7.74 (m, 1H), 7.68 (s, 1H), 7.65-7.60 (m, 1H), 3.88-3.76 (m, 2H), 3.22-3.17 (m, 1H), 3.00-2.94 (m, 1H), 2.17-2.12 (m, 2H), 2.10-1.90 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H).

[00874] Peak-2: Yield: 0.031 g, LRMS (ESI): Calcd $[M+H]^+$: 444.16 found: 444.4.

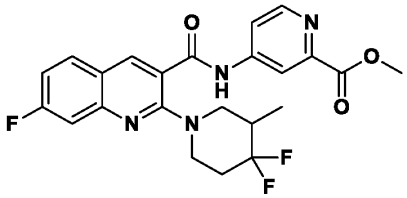
[00875] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (s, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.90-7.88 (m, 1H), 7.82-7.80 (m, 1H), 7.78-7.74 (m, 1H), 7.68 (s, 1H), 7.64-7.59 (m, 1H), 3.8-3.76 (m, 2H), 3.22-3.17 (m, 1H), 3.00-2.94 (m, 1H), 2.19-2.11 (m, 2H), 1.99-1.87 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H).

Compound 126 and 127

Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide (Peak-1 & Peak-2)



Synthesis of methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate



[00876] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxylic acid (590 mg, 1.82 mmol) in DCM (18 mL) was HATU (1.04 g, 2.7 mmol) and DMAP (670 mg, 5.5 mmol). The reaction mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added methyl 4-aminopicolinate, HCl (343 mg, 1.82 mmol). The reaction mixture was stirred at room temperature overnight. After reaction completion, the reaction mixture was concentrated and the residue was dissolved in MeCN (18 mL). The reaction mixture was heated at 65 °C for 72 hours. After reaction completion, the reaction mixture was concentrated and the residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to give methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate as a light orange powder.

Synthesis of N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamide

[00877] A round bottom flask was charged with methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-carboxamido)picolinate (920 mg, 2 mmol) and 7M ammonia in methanol (28.6 mL). The reaction mixture was heated at 50 °C for 24 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by flash column chromatography with a gradient of ethyl acetate in hexanes to give N-(2-carbamoylpyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-fluoroquinoline-3-

carboxamide as a yellow solid, which was further purified by chiral SFC to give the two enantiomers.

[00878] Peak 1: LRMS (ESI): Calcd $[M+H]^+$: 444.16 found: 444.3.

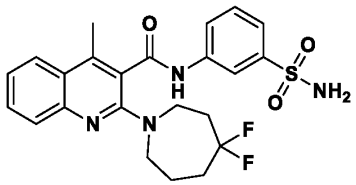
[00879] ^1H NMR (400 MHz, MeOD) δ 8.61 (d, J = 5.5 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.08 – 8.01 (m, 1H), 7.88 (dd, J = 9.2, 5.1 Hz, 1H), 7.62 – 7.50 (m, 2H), 3.94 (d, J = 13.6 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.08 – 2.97 (m, 1H), 2.29 – 2.08 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H).

[00880] Peak 2: LRMS (ESI): Calcd $[M+H]^+$: 444.16 found: 444.3.

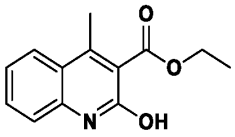
[00881] ^1H NMR (400 MHz, MeOD) δ 8.61 (d, J = 5.5 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.08 – 8.01 (m, 1H), 7.88 (dd, J = 9.2, 5.1 Hz, 1H), 7.62 – 7.50 (m, 2H), 3.94 (d, J = 13.6 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.08 – 2.97 (m, 1H), 2.29 – 2.08 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H).

Compound 128

Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methyl-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

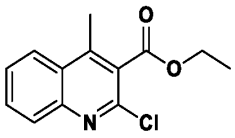


Synthesis of ethyl 2-hydroxy-4-methylquinoline-3-carboxylate



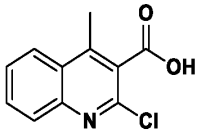
[00882] A mixture of 1-(2-aminophenyl)ethan-1-one (4.6 g, 34.1 mmol) and 1,3-diethyl propanedioate (8.18 g, 51 mmol) was heated in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene at 160 °C for 4 hours. After reaction completion, the reaction mixture was cooled to room temperature, washed with water, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-hydroxy-4-methylquinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-chloro-4-methylquinoline-3-carboxylate



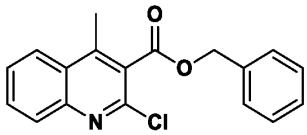
[00883] 2-hydroxy-4-methylquinoline-3-carboxylate (2.5 g, 10.8 mmol) was dissolved into phosphorus oxychloride (25 mL) at room temperature and heated to 110 °C for 12 hours. The reaction mixture was cooled to room temperature and excess phosphorus oxychloride was distilled out. The residue was dissolved into ethyl acetate and washed with sodium bicarbonate solution. The organic layers were combined, separated, washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-chloro-4-methylquinoline-3-carboxylate as a white solid.

Synthesis of 2-chloro-4-methylquinoline-3-carboxylic acid



[00884] To a solution of ethyl 2-chloro-4-methylquinoline-3-carboxylate (1.5 g, 6.0 mmol) in ethanol (30 mL) was added sodium hydroxide (0.96 g, 24 mmol) in water (30 mL) and stirred at 70 °C for 24 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, acidified with 1*N* hydrochloric solution, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-chloro-4-methylquinoline-3-carboxylic acid as an off-white solid.

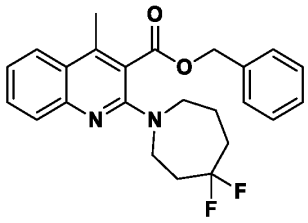
Synthesis of benzyl 2-chloro-4-methylquinoline-3-carboxylate



[00885] To a solution of 2-chloro-4-methylquinoline-3-carboxylic acid (1 g, 4.5 mmol) in *N,N*-dimethylformamide (6 mL) was added potassium carbonate (1.56 g, 11 mmol) and benzyl bromide (1.5 g, 9 mmol) dropwise at room temperature. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was quenched with ice cold water then extracted with ethyl acetate. The organic layers were combined, dried over

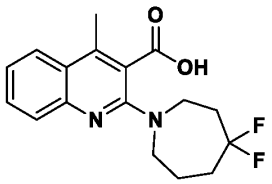
sodium sulfate, filtered, then concentrated. The residue was purified using flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford benzyl 2-chloro-4-methylquinoline-3-carboxylate as a colourless oil.

Synthesis of benzyl 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylate



[00886] To a solution of benzyl 2-chloro-4-methylquinoline-3-carboxylate (1.25 g, 4 mmol) in 1-methylpyrrolidin-2-one (5 mL) was added 4,4-difluoroazepane hydrochloride (0.83 g, 4.8 mmol) and DIPEA (2.8 mL, 16.1 mmol) dropwise in slow manner. The reaction mixture was heated at 130 °C for 24 hours. After reaction completion, the reaction mixture was quenched with ice cold water then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified using flash column chromatography with a gradient of 20 % ethyl acetate in hexane to yield the pure product as benzyl 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylate as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylic acid



[00887] To a solution of benzyl 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylate (0.45 g, 1.1 mmol) in methanol (20 mL) was added 10% palladium on carbon (0.012 g, 0.11 mmol) under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 24 hours. After reaction completion, the reaction mixture was filtered through celite pad and washed with methanol. The filtrate was concentrated and the residue was triturated with diethyl ether and pentane to afford 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylic acid as a white solid.

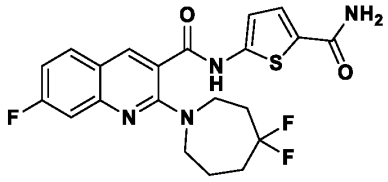
Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methyl-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

[00888] To a solution of 2-(4,4-difluoroazepan-1-yl)-4-methylquinoline-3-carboxylic acid (0.17 g, 0.53 mmol) in dichloromethane (10 mL) was added HATU (0.30 g, 0.79 mmol) and 4-(dimethylamino) pyridine (0.030 g, 0.27 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved with acetonitrile (5 mL). To this solution 3-aminobenzenesulfonamide (0.11 g, 0.64 mmol) was added. The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoroazepan-1-yl)-4-methyl-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a white solid. Yield: 0.028 g, 11%; LRMS (ESI): Calcd [M+H]+: 475.16, found: 475.25.

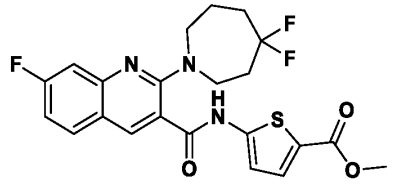
[00889] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10. 93 (s, 1H), 8.34 (s, 1H), 8.00-7.98 (m, 1H), 7.81-7.80 (m, 1H), 7.68-7.63 (m, 2H), 7.60-7.55 (m 2H), 7.44 (br s, 2H), 7.38 (t, J = 6.8, Hz, 1H), 3.78-3.72 (m, 2H), 3.71-3.68 (m, 2H), 2.59 (s, 3H), 2.35-2.32 (m, 2H), 2.07-2.01 (m, 2H), 1.86-1.84 (m, 2H).

Compound 129

Synthesis of N-(5-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

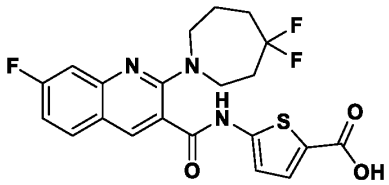


Synthesis of methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate



[00890] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.3 g, 0.9 mmol) in 1, 4- dioxane (5 mL) was added methyl 5-bromothiophene-2-carboxylate (0.25 g, 1.1 mmol), cesium carbonate (0.91 g, 2.8 mmol) was added under nitrogen atmosphere. After degassing the reaction mixture with nitrogen gas for 20 min, BrettPhos Pd G3 (0.084 g, 0.09 mmol) was added. The reaction mixture was heated at 100 ℃ for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine solution and dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexanes to afford methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate as an off-white solid.

Synthesis of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid



[00891] To a solution of methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate (0.1 g, 0.21 mmol) in tetrahydrofuran (5 mL) and methanol (0.5 mL) was added lithium hydroxide (0.037 g, 1.0 mmol) in water (1 mL) and stirred at 60 °C for 12 hours. After reaction completion, the reaction mixture was concentrated and the residue was diluted with water, acidified with 1*N* hydrochloric solution, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid as an off-white solid.

Synthesis of N-(5-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

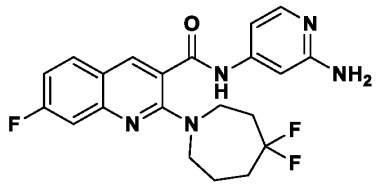
[00892] To a solution of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid (0.055 g, 0.122 mmol) in *N,N*-dimethylformamide (1 mL) was added ammonium chloride (0.065 g, 1.22 mmol), *N,N*-diisopropylethylamine (0.047 g, 0.366 mmol) and HATU (0.069 g, 0.18 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, reaction mixture was

diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(5-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.012 g, 22%; LRMS (ESI): Calcd [M+H]+: 449.13, found: 449.4.

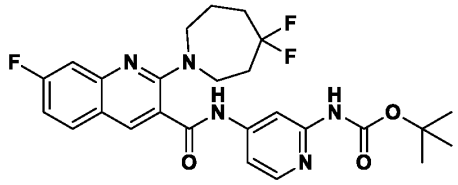
[00893] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 8.34 (s, 1H), 7.89 (dd, J = 2.0, 6.8 Hz, 1H), 7.74 (s, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.31 (dd, J = 2.4, 11.2 Hz, 1H), 7.21-7.16 (m, 1H), 7.14 (s, 1H), 6.70 (s, 1H), 3.72-3.69 (m, 2H), 3.52 (t, J = 6.0 Hz, 2H), 2.42-2.37 (m, 2H), 2.01-1.99 (m, 2H), 1.95-1.86 (m, 2H).

Compound 130

Synthesis of N-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



Synthesis of tert-butyl (4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)carbamate



[00894] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.3 g, 0.92 mmol) in 1, 4- dioxane (4 mL) was added *tert*-butyl (4-bromopyridin-2-yl)carbamate (0.3 g, 1.1 mmol) and cesium carbonate (0.9 g, 2.8 mmol). After degassing the reaction mixture with nitrogen gas for 20 min, BrettPhos Pd G3 (0.08 g, 0.092 mmol) was added and the reaction mixture was heated at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *tert*-butyl (4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)carbamate as an off-white solid.

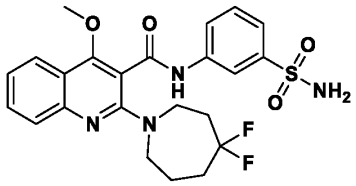
Synthesis of N-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00895] To a stirred solution of *tert*-butyl (4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)carbamate (0.17 g, 0.33 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After reaction completion, the excess trifluoroacetic acid was distilled out. The residue was dissolved into dichloromethane and washed with sodium bicarbonate solution. The organic layers were combined, separated, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as off white solid. Yield: 0.007 g, 5%; LRMS (ESI): Calcd [M+H]+: 416.17, found: 416.4.

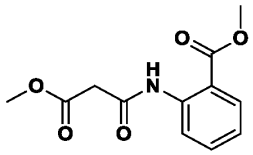
[00896] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.32 (s, 1H), 7.94-7.90 (m, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.32 (dd, J =11.2 Hz, 2.4 Hz, 1H), 7.23-7.18 (m, 1H), 6.99 (d, J = 1.2 Hz, 1H), 6.69 (dd, J = 4 Hz, 1.6 Hz, 1H), 5.93 (s, 2H), 3.75-3.72 (m, 2H), 3.58 (t, J = 6.0 Hz, 2H), 2.42-2.36 (m, 2H), 2.01-1.99 (m, 2H), 1.90-1.88 (m, 2H).

Compound 131

Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide



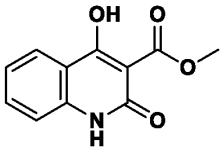
Synthesis of methyl 2-(3-methoxy-3-oxopropanamido)benzoate



[00897] To a stirred solution of methyl 2-aminobenzoate (20 g, 130 mmol) in dichloromethane (200 mL), triethylamine (92.5 mL, 265 mmol) and methyl 3-chloro-3-oxopropanoate (28.4 mL, 200 mmol) were added dropwise at 0-5 °C. The reaction mixture was warmed to room temperature and stirred at room temperature for 3 hours. After reaction

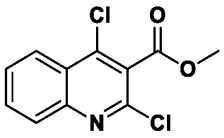
completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexane to afford methyl 2-(3-methoxy-3-oxopropanamido)benzoate as a white solid.

Synthesis of methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate



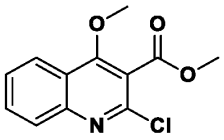
[00898] To a stirred solution of methyl 2-(3-methoxy-3-oxopropanamido)benzoate (25 g, 100 mmol) in methanol (100 mL), 20% sodium methoxide in methanol (50 mL) was added dropwise at room temperature and the reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated using diethyl ether and pentane to afford methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2,4-dichloroquinoline-3-carboxylate



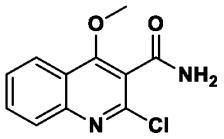
[00899] To a stirred solution of methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (5.0 g, 22.8 mmol) in phosphorus oxychloride (50 mL), triethylamine (2.77 g, 27.4 mmol) was added dropwise at room temperature. The reaction mixture was heated at 80 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, poured over crushed ice, neutralized with saturated solution of sodium bicarbonate, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 2,4-dichloroquinoline-3-carboxylate as a white solid.

Synthesis of methyl 2-chloro-4-methoxyquinoline-3-carboxylate



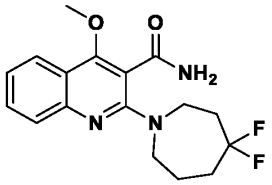
[00900] To a stirred solution of methyl 2,4-dichloroquinoline-3-carboxylate (3 g, 11.7 mmol) in methanol (50 mL), sodium methoxide (1.9 g, 35 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 20 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 10-15% ethyl acetate in hexane to afford methyl 2-chloro-4-methoxyquinoline-3-carboxylate as a white solid.

Synthesis of 2-chloro-4-methoxyquinoline-3-carboxamide



[00901] A mixture of methyl 2-chloro-4-methoxyquinoline-3-carboxylate (0.9 g, 3.6 mmol) and 7M Ammonia in methanol (10 mL) were heated at 80 °C for 16 hours. After reaction completion, the reaction mixture was concentrated. The residue was purified by flash column chromatography with a gradient of 15-20% ethyl acetate in hexane to afford 2-chloro-4-methoxyquinoline-3-carboxamide as a white solid.

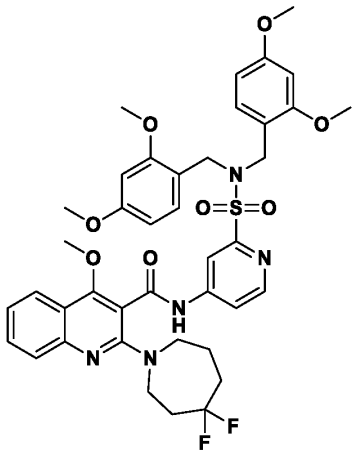
Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide



[00902] To a stirred solution of 2-chloro-4-methoxyquinoline-3-carboxamide (0.6 g, 2.5 mmol) in *N,N*-dimethylformamide (5 mL), 4,4-difluoroazepane hydrochloride (0.5 g, 3 mmol) and cesium carbonate (2.5 g, 7.6 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with

ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-25% ethyl acetate to afford 2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide as a yellow solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide



[00903] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide (0.18 g, 0.54 mmol) in 1,4-dioxane (10 mL), Pd Brettphos G3 (0.049 g), cesium carbonate (0.35 g, 1.1 mmol) and 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.29 g, 0.54 mmol) were added at 0-5 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and then heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was cooled to room temperature, diluted with water, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-25% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-4-methoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide

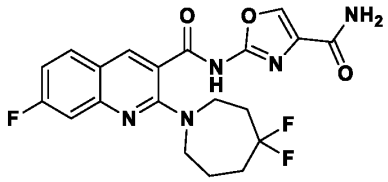
[00904] To a stirred solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-4-methoxyquinoline-3-carboxamide (0.4 g, 0.51 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.3 mL) was added dropwise at 0-5 °C. The

reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-4-methoxy-*N*-(3-sulfamoylphenyl)quinoline-3-carboxamide as a pale yellow solid. Yield: 0.10 g, 40.31%; LRMS (ESI): Calcd [M+H]+: 491.16, found: 491.05.

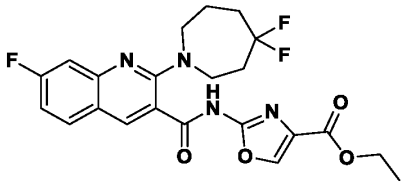
[00905] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (brs, 1H), 7.68-7.63 (m, 3H), 7.29-7.21 (m, 6H), 6.79 (s, 1H), 3.71-3.70 (m, 2H), 3.65 (s, 3H), 3.51 (t, J = 6.0 Hz, 2H), 2.44-2.37 (m, 2H), 2.08-2.02 (m, 2H), 1.92-1.90 (m, 2H).

Compound 132

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide



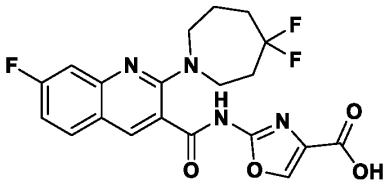
Synthesis of ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate



[00906] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.30 g, 0.92 mmol) in acetonitrile (5 mL) was added carbonyl diimidazole (0.22 g, 1.4 mmol). The reaction mixture was heated at 80 °C for 2 hours. After reaction completion, ethyl 2-aminooxazole-4-carboxylate (0.17 g, 1.1 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (0.16 g, 1.1 mmol) was added to the reaction mixture. The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to

afford ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate as a white solid.

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid



[00907] To a solution of ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate (0.2 g, 0.4 mmol) in methanol (4 mL), tetrahydrofuran (4 mL) and water (4 mL) was added lithium hydroxide monohydrate (0.04 g, 1.7 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1*N* hydrochloric acid , then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid as a white solid.

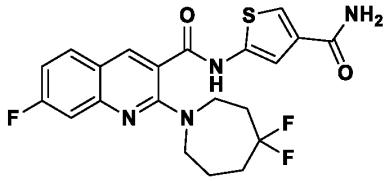
Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide

[00908] To a solution of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid (0.12 g, 0.27 mmol) in *N*, *N*-dimethylformamide (5 mL) was added HATU (0.16 g, 0.41 mmol), *N*,*N*-diisopropylethylamine (0.2 mL, 1.3 mmol) and ammonium chloride (0.14 g, 2.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the material was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide as a white solid. Yield: 0.05 g, 42%; LRMS (ESI): Calcd [M+H]+: 434.14, found: 434.21.

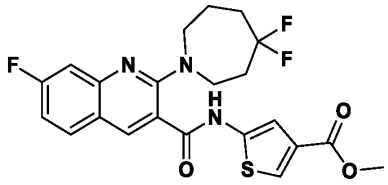
[00909] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 8.41 (s, 2H), 7.94-7.90 (m, 1H), 7.54 (br s, 1H), 7.44 (br s, 1H), 7.31 (dd, J = 2.4, 10.8 Hz, 1H), 7.23-7.18 (m, 1H), 3.73-3.72 (m, 2H), 3.53 (t, J = 5.6 Hz, 2H), 2.41-2.37 (m, 2H), 1.99-1.91 (m, 4H).

Compound 133

Synthesis of N-(4-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

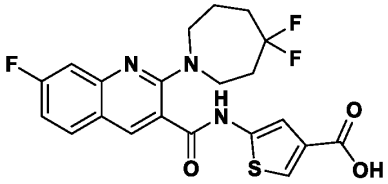


Synthesis of methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylate



[00910] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.30 g, 0.92 mmol) in dioxane (3 mL) was added methyl 5-bromothiophene-3-carboxylate (0.24 g, 1.1 mmol), cesium carbonate (0.59 g, 1.8 mmol), Xantphos (0.053 g, 0.092 mmol). The reaction mixture was degassed with nitrogen then $Pd2(dba)_3$, (0.08 g, 0.092 mmol) added and the reaction mixture heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was concentrated and diluted with brine, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylate as an off white solid.

Synthesis of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylic acid



[00911] To a solution of methyl 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylate (0.15 g, 0.32 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.06 g,

1.3 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylic acid as an off white solid.

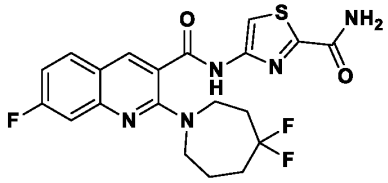
Synthesis of N-(4-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00912] To a solution of 5-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-3-carboxylic acid (0.09 g, 0.20 mmol) in *N*, *N*-dimethylformamide (4 mL) was added HATU (0.12 g, 0.30 mmol), *N*,*N*-diisopropylethylamine (0.2 mL, 1.0 mmol) and ammonium chloride (0.11 g, 2.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(4-carbamoylthiophen-2-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.010 g, 11%; LRMS (ESI): Calcd [M+H]+: 449.13, found: 449.15.

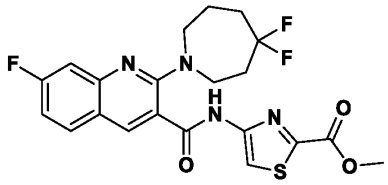
[00913] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.37 (s, 1H), 7.95-7.90 (m, 1H), 7.75 (br s, 1H), 7.65 (s, 1H), 7.34-7.31 (m, 1H), 7.23-7.18 (m, 2H), 7.10 (s, 1H), 3.78-3.72 (m, 2H), 3.53 (t, J = 6.0 Hz, 2H), 2.44-2.38 (m, 2H), 2.01-1.95 (m, 2H), 1.89-1.87 (m, 2H).

Compound 134

Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxamide

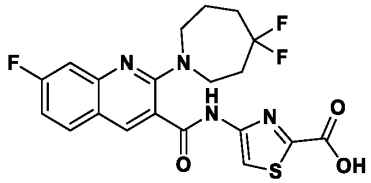


Synthesis of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylate



[00914] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.2 g, 0.62 mmol) 1, 4- dioxane (4 mL) was added methyl 4-bromothiazole-2-carboxylate (0.18 g, 0.8 mmol) and cesium carbonate (0.6 g, 1.8 mmol) was added. After degassing the reaction mixture with nitrogen gas for 20 min, Brettphos Pd G3 (0.113 g, 0.12 mmol) was added. The reaction mixture was heated at 110 °C for 12 hours. After reaction completion, the residue was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylate as an off-white solid.

Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylic acid



[00915] To a solution of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylate (0.08 g, 0.17 mmol) in tetrahydrofuran (2 mL) and methanol (0.5 mL) was added lithium hydroxide (0.029 g, 0.85 mmol) in water (1 mL) and stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, acidified with 1*N* hydrochloric solution, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylic acid as an off-white solid.

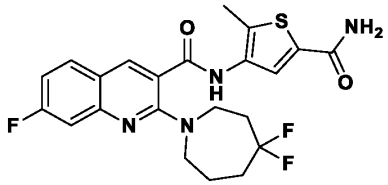
Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxamide

[00916] To a solution of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxylic acid (0.068 g, 0.15 mmol) in *N,N*-dimethylformamide (1 mL) was added ammonium chloride (0.08 g, 1.5 mmol), *N,N*-diisopropylethylamine (0.058 g, 0.45 mmol) and HATU (0.086 g, 0.22 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-60% ethyl acetate in hexane to afford 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-2-carboxamide as a white solid. Yield: 0.012 g, 17.6%; LRMS (ESI): Calcd [M+H]+: 450.12, found: 450.1.

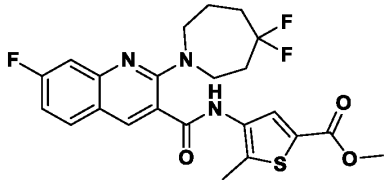
[00917] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 7.89 (dd, J = 2.4, 6.4 Hz, 1H), 7.68 (s, 1H), 7.32 (dd, J = 2.4, 8.4 Hz, 1H), 7.22-7.17 (m, 1H), 3.74-3.72 (m, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.44-2.37 (m, 2H), 2.01-1.95 (m, 2H), 1.91-1.85 (m, 2H).

Compound 135

Synthesis of N-(5-carbamoyl-2-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



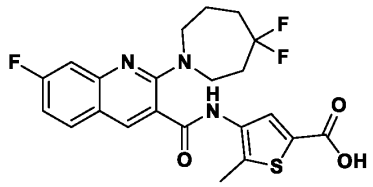
Synthesis of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylate



[00918] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.3 g, 0.93 mmol) in 1,4-dioxane (5 mL) was added methyl 4-bromo-5-methylthiophene-2-

carboxylate (0.26 g, 1.1 mmol), cesium carbonate (0.61 g, 1.9 mmol), Tris(dibenzylideneacetone)dipalladium(0) (0.085 g, 0.092 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9*H*-xanthene (Xantphos) (0.107 g, 0.18 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylate as a pale yellow solid.

Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylic acid



[00919] To a solution of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylate (0.3 g, 0.62 mmol) in methanol (5 mL), tetrahydrofuran (5 mL) was added a solution of lithium hydroxide (60 mg, 2.5 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered and filtrate was concentrated under reduced pressure to afford 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylic acid as a white solid.

Synthesis of N-(5-carbamoyl-2-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

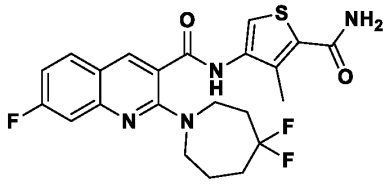
[00920] To a solution of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-5-methylthiophene-2-carboxylic acid (0.26 g, 0.56 mmol) in dichloromethane (20 mL) was added HATU (0.43 g, 1.1 mmol) and ammonium carbonate (0.54 g, 5.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was washed with brine solution and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The

residue was purified by reversed phase prep-HPLC to afford *N*-(5-carbamoyl-2-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 35 mg, 13%; LRMS (ESI): Calcd [M+H]+: 463.14, found: 463.3.

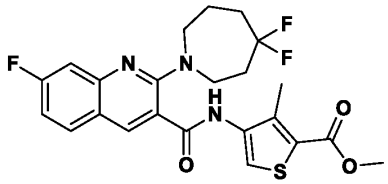
[00921] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.32 (s, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.95-7.91 (m, 2H), 7.35-7.30 (m, 2H), 7.22-7.17 (m, 1H), 3.77-3.76 (m, 2H), 3.66 (t, J = 6.0 Hz, 2H), 2.41-2.38 (m, 5H), 2.07-1.89 (m, 4H).

Compound 136

Synthesis of N-(5-carbamoyl-4-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

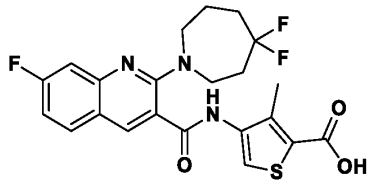


Synthesis of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylate



[00922] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.2 g, 0.6 mmol) in 1,4-dioxane (5 mL) was added methyl 4-bromo-3-methylthiophene-2-carboxylate (0.22 g, 0.9 mmol), cesium carbonate (0.4 g, 1.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.03 g, 0.03 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9*H*-xanthene (Xantphos) (0.035 g, 0.061 mmol) under nitrogen atmosphere and heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylate as a pale yellow solid.

Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylic acid



[00923] To a solution of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylate (0.1 g, 0.20 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) was added solution of lithium hydroxide (0.01 g, 0.4 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was neutralized with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated to afford 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylic acid as a white solid.

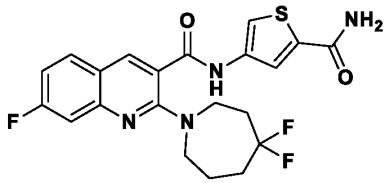
Synthesis of N-(5-carbamoyl-4-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00924] To a solution of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)-3-methylthiophene-2-carboxylic acid (0.08 g, 0.17 mmol) in dichloromethane (10 mL) was added HATU (0.16 g, 0.34 mmol) and ammonium carbonate (0.19 g, 1.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was washed with brine solution and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(5-carbamoyl-4-methylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.01 g, 12.6%; LRMS (ESI): Calcd [M+H]+: 463.14, found: 463.25.

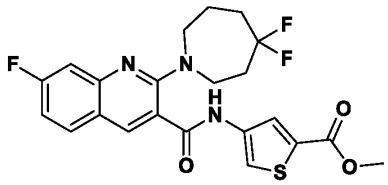
[00925] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.98 (s, 1H), 8.36 (s, 1H), 7.94-7.90 (m, 1H), 7.34-7.31 (m, 1H), 7.23-7.18 (m, 1H), 7.18-7.15 (m, 2H), 6.59 (s, 1H), 3.71-3.70 (m, 2H), 3.51 (t, J = 6.0 Hz, 2H), 2.42-2.35 (m, 5H), 2.03-1.95 (m, 2H), 1.87-1.86 (m, 2H).

Compound 137

Synthesis of N-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

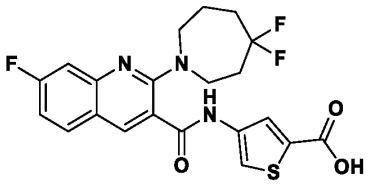


Synthesis of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate



[00926] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.25 g, 0.77 mmol) in 1,4-dioxane (4 mL) was added methyl 4-bromothiophene-2-carboxylate (0.26 g, 1.2 mmol), cesium carbonate (0.76 g, 2.3 mmol), Brettphos Pd G3 (0.07 g, 0.08 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexane to afford methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate as a pale yellow solid.

Synthesis of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid



[00927] To a solution of methyl 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate (0.1 g, 0.2 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) was added solution of lithium hydroxide (0.052 g, 2.1 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the

reaction mixture was concentrated. The residue was acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated to afford 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid as a white solid.

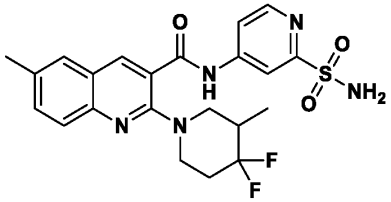
Synthesis of (N-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide

[00928] To a solution of 4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid (0.1 g, 0.2 mmol) in dichloromethane (10 mL) was added HATU (0.17 g, 0.44 mmol) and ammonium carbonate (0.21 g, 2.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the compound was washed with brine solution and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford *N*-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as a white solid. Yield: 0.02 g, 20%; LRMS (ESI): Calcd [M+H]+: 449.13, found: 449.25.

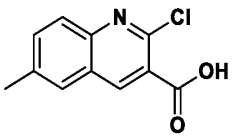
[00929] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 8.30 (s, 1H), 8.07 (br s, 1H), 7.92-7.88 (m, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.41 (br s, 1H), 7.31 (dd, J = 2.4, 13.6 Hz, 1H), 7.22-7.17 (m, 1H), 3.75-3.72 (m, 2H), 3.59 (t, J = 5.6 Hz, 2H), 2.35-2.32 (m, 2H), 2.00-1.95 (m, 2H), 1.89-1.86 (m, 2H).

Compound 138

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

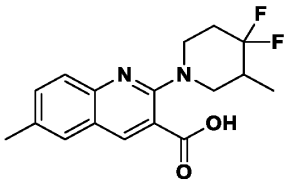


Synthesis of 2-chloro-6-methylquinoline-3-carboxylic acid



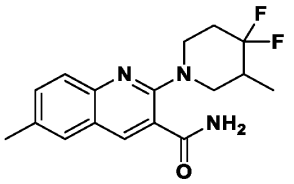
[00930] To a stirred solution of silver nitrate (1.3 g, 7.8 mmol) in water (15 ml) was added sodium hydroxide (1.56 g, 39 mmol) and reaction mixture was stirred for 30 min at room temperature. Then a solution of 2-chloro-6-methylquinoline-3-carbaldehyde (1 g, 4.9 mmol) in ethanol (30 ml) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours. After reaction completion, the reaction mixture was filtered through celite and solvent was removed in vacuo. The residue was diluted with water and acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. to afford 2-chloro-6-methylquinoline-3-carboxylic acid as a yellow solid which was used directly into next step without purification.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxylic acid



[00931] To a solution of 2-chloro-6-methylquinoline-3-carboxylic acid (0.5 g, 2.3 mmol) in *N,N*-dimethylformamide (3.6 ml) was added potassium carbonate (1.6 g, 11 mmol) and 4,4-difluoro-3-methylpiperidine hydrochloride (0.6 g, 3.4 mmol) at room temperature and the reaction mixture was heated at 110 °C for 24 hours. After reaction completion, the reaction mixture was quenched with ice cold water, acidified with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was triturated with ether and pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxylic acid as a yellow solid.

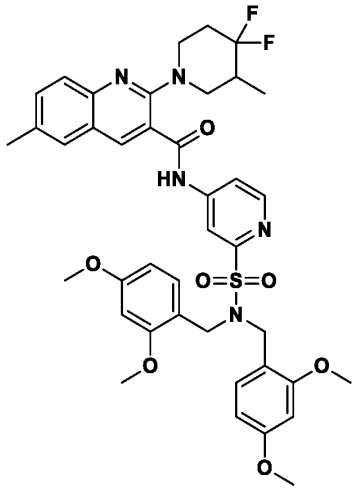
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide



[00932] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxylic acid (0.4 g, 1.25 mmol) in *N,N*-dimethylformamide (6 mL) was added *N,N*-diisopropylethyl amine (1.1 mL, 6.2 mmol), HATU (0.44 g, 1.87 mmol) and ammonium chloride (0.67 g, 12.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was quenched with ice cold water

and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-50% ethyl acetate in hexanes to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide as a yellow solid.

Synthesis of N-(2-(N, N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide



[00933] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide (0.3 g, 0.94 mmol) in 1,4-dioxane (23 mL) was added 4-bromo-*N,N*-bis[(2,4-dimethoxyphenyl)methyl]pyridine-2-sulfonamide (0.6 g, 1.1 mmol), cesium carbonate (0.92 g, 2.8 mmol). The reaction mixture was degassed with nitrogen for 15 min. Then, Brett Phos Pd G3 (0.08 g, 0.09 mmol) was added and the reaction mixture was heated at 100 °C for 12 hours. After reaction completion, reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 50-70% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

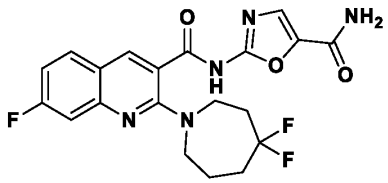
[00934] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methylquinoline-3-carboxamide (0.3 g, 0.39 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (2 mL) at 0 °C. The reaction mixture

was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was concentrated. The residue was neutralized with saturated solution of sodium bicarbonate and extracted by ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-methyl-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as an off-white solid. Yield: 0.150 g, 81%; LRMS (ESI): Calcd [M+H]+: 476.16, found: 476.05.

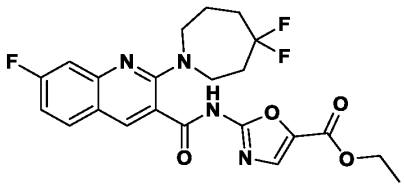
[00935] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.26 (s, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.04 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 1.6 Hz, 5.2 Hz, 1H), 7.67 (m, 2H), 7.56 (dd, J = 2.0 Hz, 8.80 Hz, 1H), 7.50 (s, 2H), 3.84-3.74 (m, 2H), 3.18 (t, J = 11.2 Hz, 1H), 2.95 (t, 10.80 Hz, 1H), 2.45 (s, 3H), 2.19-2.13 (m, 2H), 2.01-1.87 (m, 1H), 0.93 (d, J = 6.80 Hz, 3H).

Compound 139

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxamide



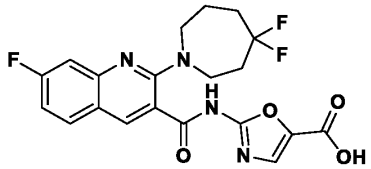
Synthesis of ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylate



[00936] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (0.30 g, 0.92 mmol) in acetonitrile (5 mL) was added carbonyl diimidazole (0.22 g, 1.4 mmol) and the reaction mixture was heated at 80 °C for 2 hours. After reaction completion, ethyl 2-aminooxazole-5-carboxylate (0.17 g, 1.1 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.16 g, 1.1 mmol) were added to the reaction mixture and the reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column

chromatography with a gradient of 45-50% ethyl acetate in hexane to afford ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylate as a white solid.

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylic acid



[00937] To a solution of ethyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylate (0.10 g, 0.21 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) and water (2 mL) was added lithium hydroxide (0.02 g, 0.9 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture as concentrated. The residue was diluted with 1*N* hydrochloric acid then extracted with ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylic acid as a white solid.

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxamide

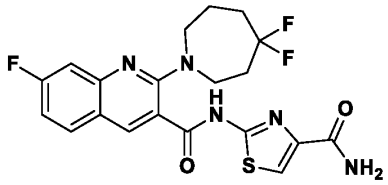
[00938] To a solution of2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxylic acid (0.08 g, 0.27 mmol) in *N*, *N*-dimethylformamide (5 mL) was added HATU (0.16 g, 0.41 mmol), *N*,*N*-diisopropylethylamine (0.2 mL, 1.3 mmol) and ammonium chloride (0.14 g, 2.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted the compound with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)oxazole-5-carboxamide as a white solid. Yield: 0.01 g, 12%; LRMS (ESI): Calcd [M+H]+: 434.14, found: 434.30.

[00939] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 8.40 (s, 1H), 7.93-7.89 (m, 1H), 7.84 (br s, 1H), 7.71 (br s, 1H), 7.53 (br s, 1H), 7.31 (dd, J = 2.4, 10.8 Hz, 1H), 7.22-7.17 (m,

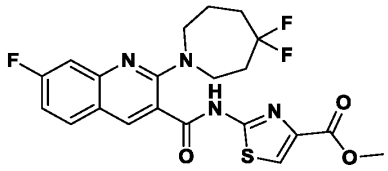
1H), 3.71-3.64 (m, 2H), 3.52 (t, J = 5.6 Hz, 2H), 2.49-2.37 (m, 2H), 1.99-1.95 (m, 2H), 1.91-1.90 (m, 2H).

Compound 140

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxamide

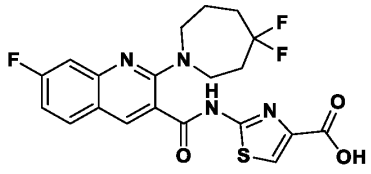


Synthesis of methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylate



[00940] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.20 g, 0.6 mmol) in dioxane (4 mL) was added methyl 2-chlorothiazole-4-carboxylate (0.13 g, 0.74 mmol), cesium carbonate (0.40 g, 1.2 mmol). The reaction mixture was degassed with nitrogen followed by the addition of tris(dibenzylideneacetone)dipalladium $Pd_2(dba)_3$ (0.006 g, 0.006 mmol) and Xantphos (0.07 g, 0.12 mmol). The reaction mixture was heated at 120 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was concentrated, diluted with water, then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylate as a white solid.

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylic acid



[00941] To a solution of methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylate (0.15 g, 0.32 mmol) in methanol (3 mL), tetrahydrofuran (3 mL) and water (3 mL) was added lithium hydroxide (0.07 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylic acid as a white solid.

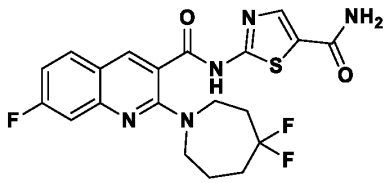
Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxamide

[00942] To a solution of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxylic acid (0.10 g, 0.22 mmol) in *N*, *N*-dimethylformamide (4 mL) was added HATU (0.13 g, 0.33 mmol), *N*,*N*-diisopropylethylamine (0.2 mL, 1.1 mmol) and ammonium chloride (0.11 g, 2.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-4-carboxamide as a white solid. Yield: 0.021 g, 21%; LRMS (ESI): Calcd [M+H]+: 450.12, found: 450.20.

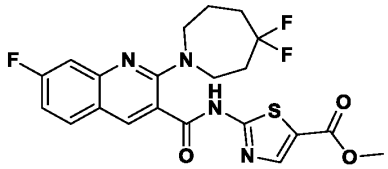
[00943] ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (s, 1H), 8.43 (s, 1H), 7.92-7.88 (m, 2H), 7.61 (br s, 1H), 7.33 (dd, J = 2.4, 10.8 Hz, 1H), 7.28 (brs, 1H), 7.22-7.19 (m, 1H), 3.71-3.69 (m, 2H), 3.47 (t, J = 5.6 Hz, 2H), 2.40-2.36 (m, 2H), 1.99-1.94 (m, 2H), 1.89-1.88 (m, 2H).

Compound 141

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxamide

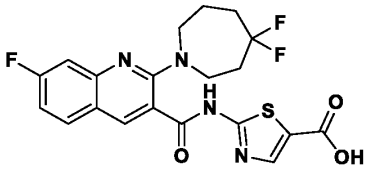


Synthesis of methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylate



[00944] To a stirred solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.3 g, 0.93 mmol) in 1,4-dioxane (30 mL), cesium carbonate (0.6 g, 1.9 mmol), Pd Brettphos G3 (0.084 g, 0.93 mmol) and methyl 2-bromothiazole-5-carboxylate (0.25 g, 1.1 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and then heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 20-30% ethyl acetate in hexane to afford methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylate as a white solid.

Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylic acid



[00945] To a stirred solution of methyl 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylate (0.2 g, 0.43 mmol) in methanol (2 mL) and tetrahydrofuran (2 mL) a solution of lithium hydroxide (0.05 g 2.2 mmol) in water (2 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. After reaction completion, organic solvents were removed under reduced pressure, neutralized with 1*N* hydrochloric acid, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with pentane to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylic acid as a white solid.

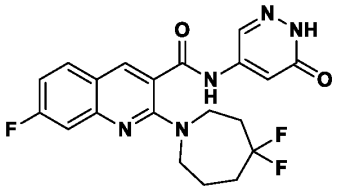
Synthesis of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxamide

[00946] To a stirred solution of 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxylic acid (0.1 g, 0.22 mmol) in dichloromethane (10 mL), HATU (0.13 g, 0.3 mmol) and ammonium carbonate (0.21 g, 2.2 mmol) were added at 0-5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After reaction completion, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)thiazole-5-carboxamide as a pale yellow solid. Yield: 0.025 g, 25%; LRMS (ESI): Calcd [M+H]+: 450.12, found: 450.00.

[00947] ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.01 (s, 1H), 8.42 (s, 1H), 8.10 (s, 1H), 7.96-7.88 (m, 2H), 7.40 (brs, 1H), 7.32 (dd, J = 10.8, 2.4 Hz, 1H), 7.22-7.17 (m, 1H), 3.70-3.69 (m, 2H), 3.46 (t, J = 6.0 Hz, 2H), 2.39-2.33 (m, 2H), 2.00-1.94 (m, 2H), 1.91-1.89 (m, 2H).

Compound 142

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(6-oxo-1,6-dihydropyridazin-4-yl)quinoline-3-carboxamide

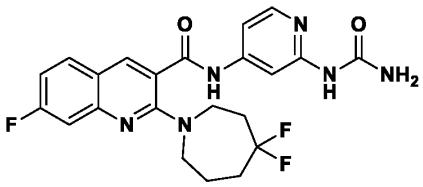


[00948] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxylic acid (250 mg, 1.16 mmol) in acetonitrile (4 mL) was added 1-(1*H*-imidazole-1-carbonyl)-1*H*-imidazole (150 mg, 0.925 mmol) and the reaction mixture was heated at 80 °C for 1 hour. After the completion of reaction, a solution of 5-aminopyridazin-3(2*H*)-one (0.1 g, 0.93 mmol) in acetonitrile and 1,8-diazabicyclo[5.4.0]-7-undecene (140 mg, 1.2 mmol) was added and the reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, then extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(6-oxo-1,6-dihydropyridazin-4-yl)quinoline-3-carboxamide as a white solid. Yield: 0.045 g, 14%; LRMS (ESI): Calcd [M+H]+: 418.15, found: 418.30.

[00949] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (s, 1H), 11.10 (s, 1H), 8.43 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.94-7.90 (m, 1H), 7.35-7.29 (m, 2H), 7.24-7.19 (m, 1H), 3.73-3.71 (m, 2H), 3.51 (t, J = 5.6 Hz, 2H), 2.44-2.32 (m, 2H), 1.98-1.94 (m, 2H), 1.90-1.89 (m, 2H).

Compound 143

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-ureidopyridin-4-yl)quinoline-3-carboxamide

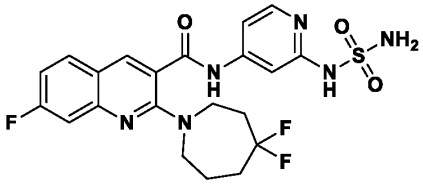


[00950] To a solution of *N*-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.2 g, 0.5 mmol) in dichloromethane (4 mL) was added *p*-nitrophenylchloroformate (0.15 g, 0.7 mmol), triethylamine (Et_3N) (0.34 mL, 2.4 mmol) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. After reaction completion the reaction mixture was charged with ammonia at -78 °C and triethylamine (0.13 mL, 0.96 mmol). The reaction mixture was warmed to room temperature then heated at 40 °C for 12 hours. After reaction completion, water was added, extracted with dichloromethane, dried over sodium sulfate, concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(2-ureidopyridin-4-yl)quinoline-3-carboxamide as a pale yellow color solid. Yield: 0.03 g, 14%; LRMS (ESI): Calcd [M+H]+: 459.2, found: 459.3.

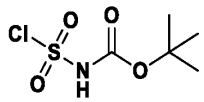
[00951] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.13 (s, 1H), 8.36 (s, 1H), 8.09 (d, J = 5.6 Hz, 1H), 7.93-7.90 (m, 1H), 7.73 (s, 1H), 7.34-7.30 (m, 2H), 7.22-7.17 (m, 1H), 6.62 (brs, 1H), 3.74-3.72 (m, 2H), 3.56 (t, J = 5.6 Hz, 2H), 2.43-2.33 (m, 2H), 2.00-1.95 (m, 2H), 1.89-1.75 (m, 3H).

Compound 144

Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(sulfamoylamino)pyridin-4-yl)quinoline-3-carboxamide

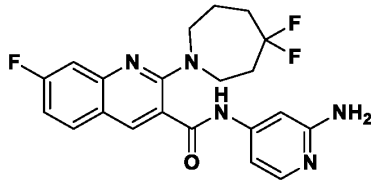


Synthesis of tert-butyl (chlorosulfonyl)carbamate



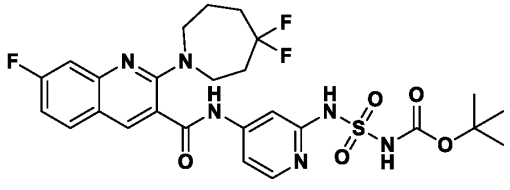
[00952] To a solution of sulfurisocyanatidic chloride (0.50 g, 3.5 mmol) in diethyl ether (10 mL) was added tert-butanol (0.4 mL, 4.2 mmol) at -78 °C. The reaction mixture was stirred for 1 hour. After reaction completion, the reaction mixture was concentrated to obtain *tert*-butyl (chlorosulfonyl)carbamate as a white solid which was used in the next step without further purification.

Synthesis of N-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide



[00953] To a solution of 2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.30 g, 0.92 mmol) in dioxane (3 mL) was added *tert*-butyl (4-aminopyridin-2-yl)carbamate (0.23 g, 1.1 mmol) and cesium carbonate (1.0 g, 2.7 mmol) under nitrogen atmosphere. After 10 min of degassing with nitrogen, BrettPhos Pd G3 (0.16 g, 0.184 mmol) was added and the reaction mixture was heated at 120 °C for 12 hours. After reaction completion, the reaction mixture was concentrated, washed with brine, then extracted the compound with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with 60-70% ethyl acetate/heptane to afford *N*-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide as brown solid.

Synthesis of tert-butyl (N-(4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)sulfamoyl)carbamate



[00954] To a suspension of sodium hydride (0.05 g, 0.96 mmol) in tetrahydrofuran (2 mL) was added solution of *N*-(2-aminopyridin-4-yl)-2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamide (0.2 g, 0.48 mmol) followed by addition of *tert*-butyl (chlorosulfonyl)carbamate (0.20 g, 0.96 mmol) in tetrahydrofuran (2 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, brine solution was added and the mixture was extracted with ethyl acetate to afford *tert*-butyl (*N*-(4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)sulfamoyl)carbamate as white solid which was used into next step without further purification.

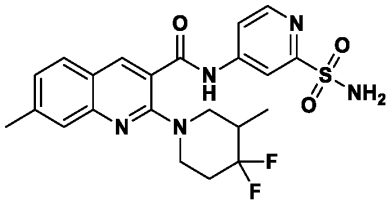
Synthesis of 2-(4,4-difluoroazepan-1-yl)-7-fluoro-N-(2-(sulfamoylamino)pyridin-4-yl)quinoline-3-carboxamide

[00955] To a solution of *tert*-butyl (*N*-(4-(2-(4,4-difluoroazepan-1-yl)-7-fluoroquinoline-3-carboxamido)pyridin-2-yl)sulfamoyl)carbamate (0.20 g, 0.33 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, neutralized with saturated sodium bicarbonate solution, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by prep HPLC to afford 2-(4,4-difluoroazepan-1-yl)-7-fluoro-*N*-(2-(sulfamoylamino)pyridin-4-yl)quinoline-3-carboxamide as a pale yellow color. Yield: 0.004 g, 2.4%; LRMS (ESI): Calcd [M+H]+: 495.14, found: 495.3.

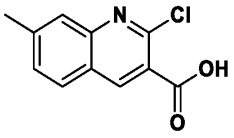
[00956] ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.32 (s, 1H), 7.94-7.90 (m, 2H), 7.33-7.30 (m, 2H), 7.21-7.16 (m, 1H), 6.95 (br s, 2H), 6.05 (br s, 2H), 3.74-3.73 (m, 2H), 3.57 (t, J = 5.6 Hz, 2H), 2.41-2.32 (m, 2H), 1.98-1.95 (m, 2H), 1.89-1.88 (m, 2H).

Compound 145

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

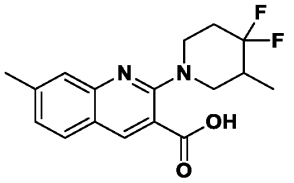


Synthesis of 2-chloro-7-methylquinoline-3-carboxylic acid



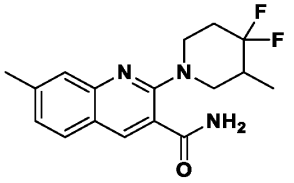
[00957] To a stirred solution of 2-chloro-7-methylquinoline-3-carbaldehyde (1.0 g, 4.8 mmol) in ethanol (10 mL) was added silver nitrate (1.3 g, 7.8 mmol) and a solution of sodium hydroxide (0.96 g, 24 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 5 hours. After reaction completion, the reaction mixture was filtered through celite and solvent was removed under reduced pressure. The residue was diluted with water followed by acidification with 1*N* hydrochloric acid and extraction with ethyl acetate. The organic layers were combined, separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-chloro-7-methylquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxylic acid



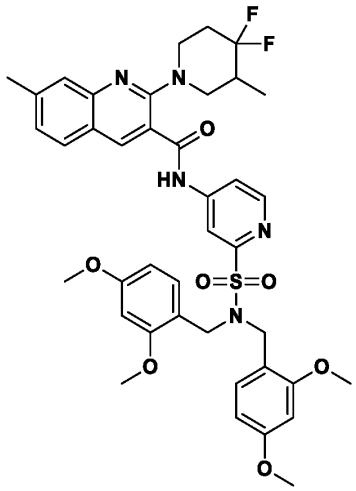
[00958] To a solution of 2-chloro-7-methylquinoline-3-carboxylic acid (1.0 g, 4.5 mmol) in *N*,*N*-dimethylformamide (10 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (1.1 g, 6.7 mmol) and potassium carbonate (3.1 g, 22.5 mmol). The reaction mixture was heated at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with ice-cold water followed by acidification with 1*N* hydrochloric acid and extraction with ethyl acetate. The combined organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxylic acid as a white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide



[00959] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxylic acid (0.7 g, 2.2 mmol) in *N*,*N*-dimethylformamide (7 mL) was added HATU (1.1 g, 3.3 mmol), *N*, *N*-diisopropylethylamine (2 mL, 10.5 mmol) and ammonium chloride (1.1 g, 22 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash chromatography with 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide



[00960] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide (0.6 g, 1.8 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (1.2 g, 2.2 mmol), cesium carbonate (1.1 g, 3.6 mmol) and BrettPhos Pd G3 (0.15 g, 0.18 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide as a white solid.

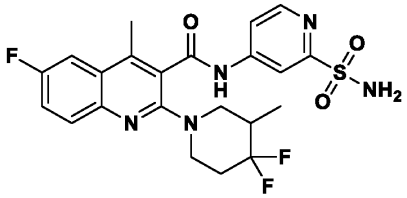
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00961] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methylquinoline-3-carboxamide (0.4 g, 0.5 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was dissolved in ethyl acetate and washed with saturated solution of sodium bicarbonate. The organic layers were combined, separated, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-7-methyl-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a white solid. Yield: 0.05 g, 20%; LRMS (ESI): Calcd [M+H]+: 476.16, found: 476.3.

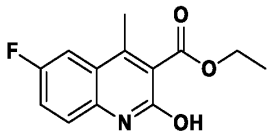
[00962] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.24 (s, 1H), 8.63 (d, J = 5.6 Hz, 1H), 8.43 (s, 1H), 8.37 (d, J = 1.2 Hz, 1H), 7.85 (dd, J = 2, 5.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.48 (s, 2H), 7.26 (d, J = 9.2 Hz, 1H), 3.85-3.73 (m, 2H), 3.22-3.17 (m, 1H), 2.98-2.93 (m, 1H), 2.50 (s, 3H), 2.23-2.11 (m, 2H), 2.04-1.81 (m, 1H), 0.92 (d, J = 8.0, 3H).

Compound 146

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide



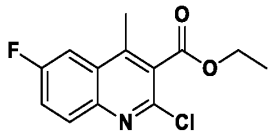
Synthesis of ethyl 6-fluoro-2-hydroxy-4-methylquinoline-3-carboxylate



[00963] To a solution of 1-(2-amino-5-fluorophenyl)ethan-1-one (3 g, 19.6 mmol) in 1,8-diazabicyclo(5.4.0)undec-7-ene (1.5 g, 9.8 mmol) was added 1,3-diethyl propanedioate (4.7 g, 29 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature and then heated at 160 °C for 3 hours. After reaction completion, the reaction

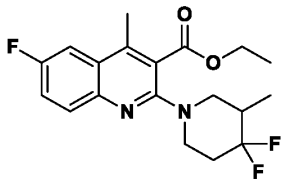
mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with diethyl ether and pentane and dried under vacuum to afford ethyl 6-fluoro-2-hydroxy-4-methylquinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-chloro-6-fluoro-4-methylquinoline-3-carboxylate



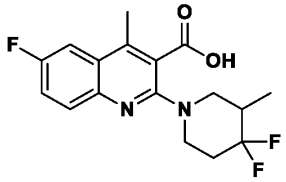
[00964] To a round bottom flask containing of ethyl 6-fluoro-2-hydroxy-4-methylquinoline-3-carboxylate (1.2 g, 4.8 mmol) was added phosphorus oxychloride (12 mL) at room temperature. The reaction mixture was heated at 110 °C for 12 hours. After reaction completion, the reaction mixture was cooled to room temperature and excess phosphorus oxychloride was distilled out. The residue was dissolved into ethyl acetate and washed with aqueous sodium bicarbonate solution. The organic layers were combined, separated, washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-chloro-6-fluoro-4-methylquinoline-3-carboxylate as brown solid.

Synthesis of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylate



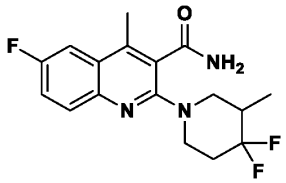
[00965] To a solution of ethyl 2-chloro-6-fluoro-4-methylquinoline-3-carboxylate (0.5 g, 1.9 mmol) in *N*,*N*-dimethylformamide (15 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (0.38 g, 2.8 mmol) and potassium carbonate (1 g, 7.5 mmol) at room temperature. The reaction mixture was heated at 120 °C for 24 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexanes to afford ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylate as a pale yellow solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylic acid



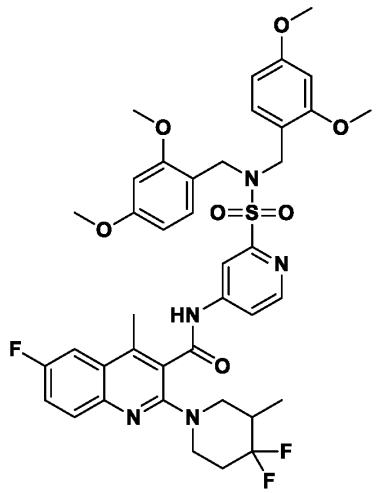
[00966] To a solution of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylate (0.34 g, 0.9 mmol) in ethanol (20 mL) was added potassium hydroxide (0.21 g, 3.7 mmol) in water (20 mL). The reaction mixture was stirred at 80 °C for 24 hours. After reaction completion, the reaction mixture was concentrated, diluted with water, acidified with 1*N* hydrochloric solution, then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylic acid as an off-white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide



[00967] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxylic acid (0.2 g, 0.6 mmol) in dichloromethane (20 mL) was added HATU (0.34 g, 0.9 mmol) and ammonium carbonate (0.57 g, 5.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was washed with brine solution and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 30-40% ethyl acetate in hexane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide as a white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide



[00968] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide (0.15 g, 0.45 mmol) in 1,4-dioxane (10 mL) was added 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (0.36 g, 0.67 mmol), cesium carbonate (0.44 g, 1.3 mmol) and BrettPhos Pd G3 (0.04 g, 0.05 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography with a gradient of 40-50% ethyl acetate in hexane to afford *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide as a light pink solid.

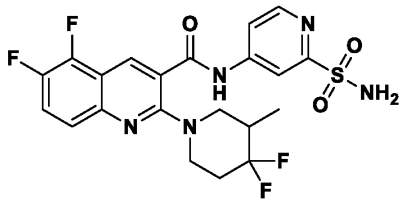
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methyl-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00969] To a solution of *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methylquinoline-3-carboxamide (0.15 g, 0.19 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (3 mL) at 0 °C . The reaction mixture was brought from 0 °C to room temperature and stirred for 12 hours. After reaction completion, The reaction mixture was concentrated and the residue was purified reversed phase prep-HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-4-methyl-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as white solid. Yield: 0.034 g, 36%; LRMS (ESI): Calcd [M+H]+: 494.15, found: 493.9.

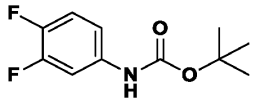
[00970] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (br s, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.35 (br s, 1H), 7.86-7.80 (m, 3H), 7.66-7.61 (m, 1H), 7.49 (br s, 2H) 3.82-3.79 (m, 1H), 3.73-3.70 (m, 1H), 3.21-3.16 (m, 1H), 3.00-2.94 (m, 1H), 2.59 (s, 3H), 2.11-2.06 (m, 2H), 1.95-1.82 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H).

Compound 147

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

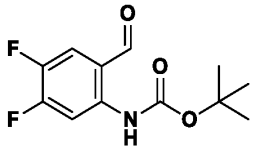


Synthesis of tert-butyl (3,4-difluorophenyl)carbamate



[00971] To a stirred solution of 3,4-difluoroaniline (5 g, 39 mmol) in dichloromethane (40 mL) was added triethylamine (7.8 g, 77.5 mmol) at room temperature and stirred for 5 minutes. The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (11 g, 50.3 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 5 hours. After reaction completion, water was added and the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated to afford *tert*-butyl-3,4-difluorophenylaminoformylate as brown solid, which was used directly for the next step without further purification.

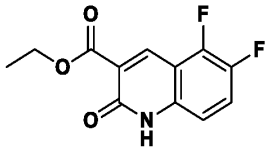
Synthesis of tert-butyl (4,5-difluoro-2-formylphenyl)carbamate



[00972] A solution of *tert*-butyl-3,4-difluorophenylaminoformylate (1 g, 4.4 mmol) in anhydrous tetrahydrofuran (15 mL) under nitrogen atmosphere was cooled to -78 °C and 2.5M *n*-butyllithium in hexane (3.8 mL, 9.6 mmol) was added dropwise. The reaction mixture was stirred for 40 minutes. After reaction completion, anhydrous *N*,*N*-dimethylformamide (0.5 mL,

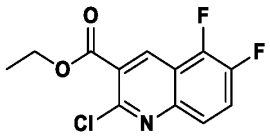
6.5 mmol) was added and the reaction mixture was stirred for 1 hour. After reaction completion, the reaction mixture was quenched with aqueous ammonium chloride solution, diluted with water, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 10% ethyl acetate in hexane to obtain *tert*-butyl (3,4-difluoro-2-formylphenyl)carbamatedehyde as an off-white solid

Synthesis of ethyl 5,6-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate



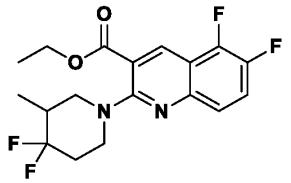
[00973] A solution of *tert*-butyl (3,4-difluoro-2-formylphenyl)carbamatedehyde (950 mg, 3.7 mmol) and diethyl malonate (770 mg, 4.8 mmol) in ethanol (10 mL), was added piperidine (63 mg, 0.73 mmol). The reaction mixture was heated at 80 °C for 12 hours. After reaction completion, the reaction mixture was filtered and the cake was washed with pentane to afford ethyl 5,6-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate as an off white solid, which was used in next step without further purification.

Synthesis of ethyl 2-chloro-5,6-difluoroquinoline-3-carboxylate



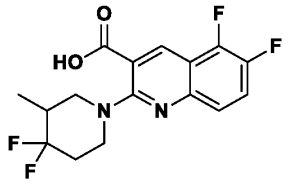
[00974] A mixture of ethyl 5,6-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate (0.65 g, 2.6 mmol) was dissolved in phosphorus oxychloride (5 mL) at room temperature. The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was then cooled to room temperature and excess of phosphorus oxychloride was distilled out. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layers were separated, washed with brine solution, dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-chloro-5,6-difluoroquinoline-3-carboxylate as a white solid.

Synthesis of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxylate



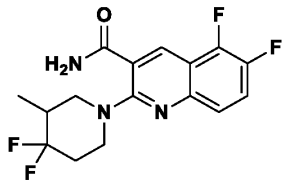
[00975] To a stirred solution of ethyl 2-chloro-5,6-difluoroquinoline-3-carboxylate (450 mg, 1.7 mmol) in toluene (10 mL) was added 4,4-difluoro-3-methylpiperidine-hydrochloride (425 mg, 2.5 mmol) and potassium carbonate (690 mg, 5 mmol). The reaction mixture was heated at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxylate as white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxylic acid



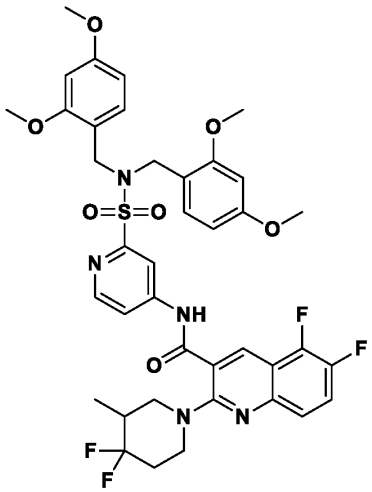
[00976] To a stirred solution of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxylate (550 mg, 1.5 mmol) in tetrahydrofuran (6 mL) and methanol (1 mL), a solution of lithium hydroxide monohydrate (550 mg, 14.8 mmol) in water (3 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water, acidified with 1N hydrochloric solution, then extracted with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and concentrated. The residue triturated with diethyl ether and *n*-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxylic acid as an off white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide



[00977] To a solution of 2-(4,4-difluoro-3-methyl-1-piperidyl)-5,6-difluoro-3-quinolinecarboxylic acid (350 mg, 1 mmol) in *N,N*-dimethylformamide (7 mL) was added HATU (583 mg, 1.53 mmol), *N,N*-diisopropylethylamine (660 mg, 5.1 mmol), and ammonium chloride (550 mg, 10 mmol). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 50% ethyl acetate in hexane to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide as pale yellow solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide



[00978] A solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide (200 mg, 0.6 mmol) and 4-bromo-*N,N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (470 mg, 0.88 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate (576 mg,1.8 mmol). The reaction mixture was degassed with nitrogen then BrettPhos Pd G3 (106 mg, 0.1 mmol) was added. The reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 50% ethyl acetate in hexane to obtain *N*-(2-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide as a pale yellow solid

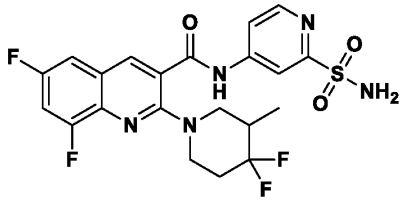
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00979] To stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoroquinoline-3-carboxamide (0.3 g, 0.38 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1.5 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated. The residue was washed with water and ether followed by filtration, and purification by Prep-HPLC to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-5,6-difluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide was obtained as pale yellow solid. Yield: 0.042 g, 22%; LRMS (ESI): Calcd [M+H]+: 498.12, found: 498.1.

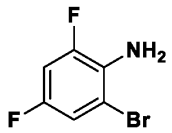
[00980] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.44 (br s, 1H), 8.59 (br s, 1H), 8.47 (s, 1H), 8.31 (s, 1H), 7.80 (s, 1H), 7.69-7.64 (m, 1H), 7.60-7.53 (m, 1H), 7.44-7.41 (m 1H), 3.97-3.93 (m, 1H), 3.90-3.83 (m, 1H), 3.27-3.21 (m, 1H), 3.04-2.98 (m, 1H), 2.18-2.15 (m, 2H), 2.07-1.89 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H).

Compound 148

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

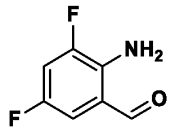


Synthesis of 2-bromo-4,6-difluoroaniline



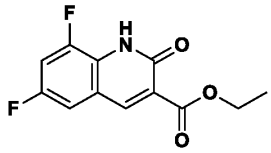
[00981] To a stirred solution of 2,4-difluoroaniline (1.3 g, 10 mmol) in acetic acid (7.5 mL) at 0 °C, a solution of bromine (0.52 mL) in acetic acid (2.5 ml) was added dropwise under stirring over a period of 30 minutes. After reaction completion of addition, sodium acetate (490 mg, 6 mmol) in water (5 mL) was added to the reaction mixture. After reaction completion, the reaction mixture was poured into ice cold water. The solid was collected by filtration and dried under vacuum to obtain 2-bromo-4,6-difluoroaniline as a brown solid.

Synthesis of 2-amino-3,5-difluorobenzaldehyde



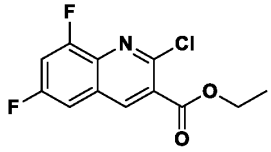
[00982] A solution of 2-bromo-4,6-difluoroaniline (2.3 g, 11 mmol) in anhydrous tetrahydrofuran (30 mL) under nitrogen atmosphere was cooled to -78 °C. 2.5 M *n*-butyllithium in hexane (9.8 mL, 24.3 mmol) was added dropwise. The reaction mixture was stirred for 40 minutes at -78 °C. After 40 minutes of stirring, *N*,*N*-dimethylformamide (1.3 mL, 17 mmol) was added and the reaction mixture was stirred for 1 hour at -78 °C. After reaction completion, aqueous ammonium chloride solution (5 mL) was added to the reaction mixture. The reaction mixture diluted with water then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography using 10% ethyl acetate in hexane to obtain 2-amino-3,5-difluorobenzaldehyde as a yellow solid

Synthesis of ethyl 6,8-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate



[00983] A solution of 2-amino-3,5-difluorobenzaldehyde (660 mg, 4.2 mmol) and diethyl malonate (875 mg, 5.46 mmol) in ethanol (15 mL), was added piperidine (71.5 mg, 0.84 mmol). The reaction mixture was refluxed for 12 hours. After reaction completion, the solid was filtered and washed with pentane to afford ethyl 6,8-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate as an off white solid, which was used in the next step without further purification.

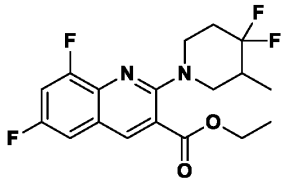
Synthesis of ethyl 2-chloro-6,8-difluoroquinoline-3-carboxylate



[00984] A mixture of ethyl 6,8-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate (0.8 g, 3.2 mmol) was dissolved in phosphorus oxychloride (5 mL) and the reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was then cooled to room temperature and excess phosphorus oxychloride was distilled out. The residue was

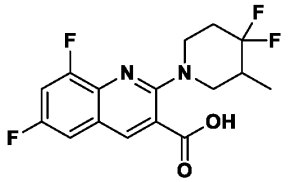
dissolved into ethyl acetate and washed with sodium bicarbonate solution. The organic layers were combined, washed with brine solution, dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-chloro-6,8-difluoroquinoline-3-carboxylate as white solid.

Synthesis of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylate



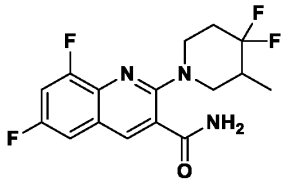
[00985] To a stirred solution of ethyl 2-chloro-6,8-difluoroquinoline-3-carboxylate (570 mg, 2.1 mmol) in toluene (10 mL) was added 4,4-difluoro-3-methylpiperidine hydrochloride (43 mg, 2.5 mmol) and potassium carbonate (870 mg, 6.29 mmol). The reaction mixture was stirred at 100 °C for 12 hours under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and pentane to afford ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylate as an off-white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylic acid



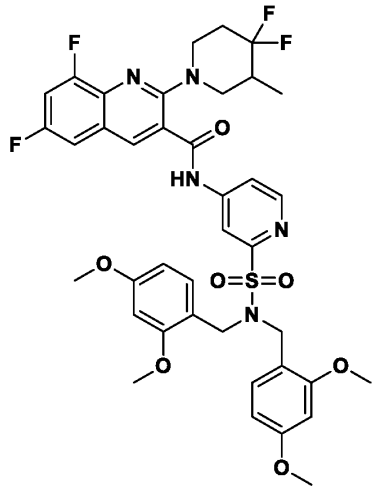
[00986] To a stirred solution of ethyl 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylate (680 mg, 1.84 mmol) in tetrahydrofuran (6 mL) and methanol (1 mL), a solution of lithium hydroxide monohydrate (680 mg, 18.4 mmol) in water (3 mL) was added. The reaction mixture was stirred at room temperature for 12 h. After reaction completion, the reaction mixture was concentrated, diluted with water, acidified with 1N hydrochloric solution, then extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was triturated with diethyl ether and *n*-pentane to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylic acid as an off white solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide



[00987] To a solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylic acid (350 mg, 1 mmol) in *N*,*N*-dimethylformamide (7 mL) was added HATU (580 mg, 1.5 mmol) at 0 °C. After 5 mins, *N*,*N*-diisopropylethylamine (660 mg, 5.1 mmol) and ammonium chloride (550 mg, 10.2 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography using 50% ethyl acetate in hexane to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide as a pale yellow solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide



[00988] A solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide (200 mg, 0.6 mmol) and 4-bromo-*N*,*N*-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (470 mg, 0.9 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate (576 mg, 1.77 mmol). The resulting solution was degassed with nitrogen for 10 minutes followed by addition of BrettPhos Pd G3 (106 mg, 0.1 mmol). The reaction mixture was heated at 100

°C for 16 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by flash column chromatography using 50% ethyl acetate in hexane to obtain *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide as an pale yellow solid.

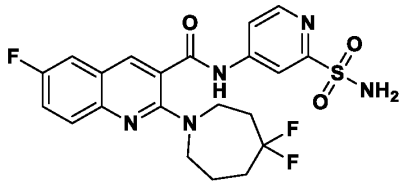
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

[00989] To stirred solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxamide (0.3 g, 376 µmol) in dichloromethane (10 mL) was added trifluroacetic acid (1.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After reaction completion, reaction mixture was concentrated. The residue was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep. HPLC to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,8-difluoro-*N*-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide was obtained as pale yellow solid. Yield: 0.015 g, 8%; LRMS (ESI): Calcd [M+H]+: 498.12, found: 498.3.

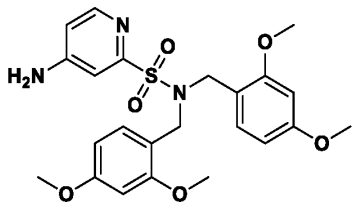
[00990] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.44 (s, 1H), 8.63 (d, J = 3.2 Hz, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 7.84 (d, J = 4.0 Hz, 1H), 7.72-7.76 (m, 1H), 7.63-7.34 (m, 3H), 3.94-3.91 (m, 1H), 3.84-3.81 (m, 1H), 3.26-3.21 (m, 1H), 3.05-2.99 (m, 1H), 2.21-2.15 (m, 2H), 2.03-1.93 (m, 1 H), 0.92 (d, J = 6.8 Hz, 3H).

Compound 149

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

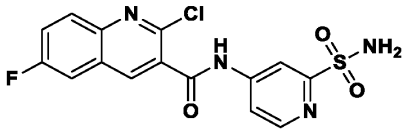


Synthesis of 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide



[00991] To a solution of 4-bromo-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (8.6 g, 16 mmol) in dioxane (53 mL) was added cesium carbonate (13 g, 40 mmol), formamide (9.6 mL, 240 mmol), and BrettPhos (1.29 g, 2.4 mmol) under nitrogen atmosphere. The reaction mixture was degassed using nitrogen then BrettPhos Pd G3 (2.18 g, 2.4 mmol) was added. The reaction mixture was heated at 100 °C for 18 hours. After reaction completion, the reaction mixture was diluted with ethyl acetate and filtered with Celite. The filtrate was concentrated and the reaction mixture was purified by flash column chromatography to give 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide as a beige powder.

Synthesis of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide



[00992] To a solution of 2-chloro-6-fluoroquinoline-3-carboxylic acid (1.4 g, 6.3 mmol) in ethyl acetate (26 mL) was added 4-amino-N,N-bis(2,4-dimethoxybenzyl)pyridine-2-sulfonamide (2.5 g, 5.3 mmol), 1-methylmidazole (1.25 mL, 15.8 mmol), and 50% T3P in ethyl acetate (6.25 mL, 10.6 mmol). The reaction temperature was stirred at room temperature for 24 hours. After reaction completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, then concentrated. The residue was purified by flash column chromatography to give 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a beige powder.

Synthesis of 2-(4,4-difluoroazepan-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

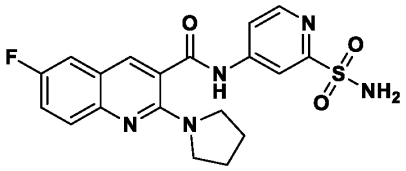
[00993] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMF (2.1 mL) was added 4,4-difluoroazepane hydrochloride (18 mg, 0.1 mmol) and potassium carbonate (44 mg, 0.32 mmol). The reaction mixture was heated at 80 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(4,4-

difluoroazepan-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.014 g, 28%; LRMS (ESI): Calcd [M+H]+: 480.13, found:480.1.

[00994] ^{1}H NMR (400 MHz, CDCl3) δ 10.70 – 10.64 (m, 1H), 8.24 – 8.19 (m, 1H), 8.04 – 7.98 (m, 1H), 7.83 (d, *J* = 4.5 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.43 – 7.34 (m, 1H), 7.01 – 6.96 (m, 2H), 6.45 (s, 2H), 3.48 – 3.43 (m, 2H), 3.27 – 3.23 (m, 2H), 2.11 – 2.07 (m, 2H), 1.51 – 1.46 (m, 4H).

Compound 150

Synthesis of 6-fluoro-2-(pyrrolidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

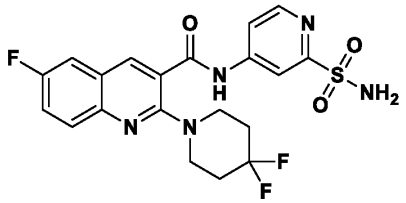


[00995] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMSO (2.1 mL) was added pyrrolidine (9 mg, 0.13 mmol) and DIPEA (73 µL, 0.42 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-2-(pyrrolidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow oil. Yield: 0.0021 g, 4.8%; LRMS (ESI): Calcd [M+H]+: 416.12, found: 416.3.

[00996] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.28 – 8.19 (m, 1H), 8.10 – 7.99 (m, 1H), 7.79 – 7.61 (m, 2H), 7.52 (d, J = 1.8 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.09 – 6.93 (m, 2H), 6.44 – 6.38 (m, 1H), 3.33 – 3.17 (m, 2H), 1.72 – 1.55 (m, 2H), 1.06 – 0.82 (m, 2H), 0.62 – 0.45 (m, 2H).

Compound 151

Synthesis of 2-(4,4-difluoropiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

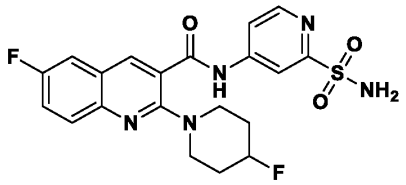


[00997] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMSO (2.1 mL) was added 4,4-difluoropiperidine hydrochloride (20 mg, 0.13 mmol) and DIPEA (73 µL, 0.42 mmol). The reaction mixture was heated at 100 ºC for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(4,4-difluoropiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.0067 g, 13.7%; LRMS (ESI): Calcd [M+H]+: 466.12, found: 466.3.

[00998] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.81 (s, 1H), 8.64 (d, *J* = 5.4 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.98 – 7.90 (m, 2H), 7.60 – 7.47 (m, 2H), 5.21 (s, 2H), 3.57 (dd, *J* = 6.9, 4.7 Hz, 4H), 2.30 – 2.16 (m, 4H).

Compound 152

Synthesis of 6-fluoro-2-(4-fluoropiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

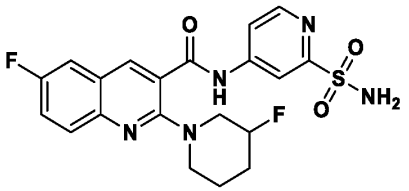


[00999] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (50 mg, 0.13 mmol) in DMSO (0.66 mL) was added 4-fluoropiperidine hydrochloride (22 mg, 0.16 mmol) and DIPEA (91.5 µL, 0.53 mmol). The reaction mixture was heated at 100 ºC for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-2-(4-fluoropiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a yellow powder. Yield: 0.5 mg, 0.9%; LRMS (ESI): Calcd $[M+H]^+$: 448.12, found: 448.3.

[001000] ^{1}HNMR(400 MHz, $CDCl_3$): δ 11.84 (s, 1H), 8.87 (s, 1H), 8.46 (d, J = 6.0 Hz, 1H), 8.20 (d, J = 1.6 Hz, 1H), 8.03(dd, J = 3.2, 2.0 Hz, 1H), 7.97 (dd, J = 5.2, 4.0, 1H), 7.56 (m, 2H), 5.11 (s, 2H), 5.02 (m, 1H), 4.89 (m, 1H), 3.56 (m, 2H), 3.36 (m, 2H), 2.12(m, 3H).

Compound 153

Synthesis of 6-fluoro-2-(3-fluoropiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

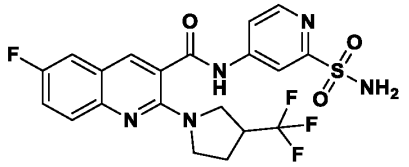


[001001] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (50 mg, 0.13 mmol) in DMF (0.66 mL) was added 3-fluoropiperidine hydrochloride (22 mg, 0.16 mmol) and DIPEA (91.5 µL, 0.53 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-2-(3-fluoropiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a beige powder. Yield: 5.1 mg, 8.7%; LRMS (ESI): Calcd $[M+H]^+$: 448.12, found: 448.3.

[001002] ^{1}H NMR(400 MHz, $CDCl_3$): δ 12.62 (s, 1H), 8.97 (s, 1H), 8.61 (d, J = 5.6 Hz, 1H), 8.54 (d, J = 2 Hz, 1H), 8.09 (dd, J = 3.6, 2.0 Hz, 1H), 7.97 (dd, J = 5.2, 4.0 1H), 7.57 (m, 2H), 5.42 (s, 2H), 5.21 (m, 1H), 5.09 (m, 1H), 3.72 (m, 1H), 3.50 (d, J = 13.2 Hz, 1H), 3.41 (m, 2H), 3.03 (t, J = 11.1, 1H), 1.80 (m, 2H).

Compound 154

Synthesis of 6-fluoro-N-(2-sulfamoylpyridin-4-yl)-2-(3-(trifluoromethyl)pyrrolidine-1-yl)quinoline-3-carboxamide



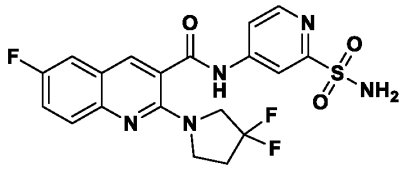
[001003] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (50 mg, 0.13 mmol) in DMF (0.66 mL) was added 3-(trifluoromethyl)pyrrolidine hydrochloride (28 mg, 0.16 mmol) and potassium carbonate (73 mg, 0.56 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-N-(2-sulfamoylpyridin-4-yl)-2-(3-(trifluoromethyl)pyrrolidine-1-yl)quinoline-3-carboxamide as a off-white powder. Yield: 0.0076 g, 12%; LRMS (ESI): Calcd [M+H]+: 484.1, found: 484.1.

[001004] ^{1}H NMR(400 MHz, DMSO-d6): δ 11.42 (s, 1H), 8.62 (d, J = 5.6 Hz, 1H), 8.40 (s, 1H), 8.32 (d, J = 1.6 Hz, 1H), 7.85(dd, J = 3.2, 2.0 Hz, 1H), 7.70 (dd, J = 5.2, 4 Hz, 1H), 7.64 (dd, J = 5.2, 2.8 Hz, 1H), 7.54 (td, J = 8.8, 2.8 Hz, 1H), 7.45 (s, 1H), 3.80 (dd, J = 11.2, 8.4 Hz,

1H), 3.66 (dd, J = 6.4, 6.0 Hz, 1H), 3.57 (m, 1H) 2.22 (sext, J = 7.6 Hz, 1H), 2.04 (sext, J = 7.6 Hz, 1H).

Compound 155

Synthesis of 2-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

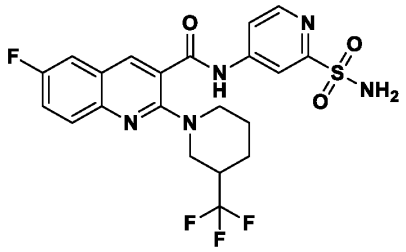


[001005] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (50 mg, 0.13 mmol) in DMF (0.66 mL) was added 3,3-difluoropyrrolidine hydrochloride (23 mg, 0.16 mmol) and potassium carbonate (73 mg, 0.56 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.001 g, 1.7%; LRMS (ESI): Calcd [M+H]+: 452.1, found: 452.2.

[001006] ^{1}H NMR(400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.65 (m, 2H), 8.21 (d, J = 1.6 Hz, 1H), 7.97 (dd, J = 3.6, 2.4 Hz, 1H), 7.91 (dd, J = 5.2, 4.0 Hz, 1H), 7.54 (m, 1H), 7.47 (m, 1H), 5.02 (s, 2H), 3.88 (t, J = 12 Hz, 2H), 3.72 (t, J = 7.6 Hz, 2H), 2.51 (sext, J = 7.2 Hz, 1H).

Compound 156

Synthesis of 6-fluoro-N-(2-sulfamoylpyridin-4-yl)-2-(3-(trifluoromethyl)piperidin-1-yl)quinoline-3-carboxamide



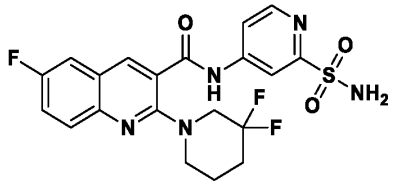
[001007] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (50 mg, 0.13 mmol) in DMSO (1.3 mL) was added 3-(trifluoromethyl)piperidine hydrochloride (30 mg, 0.16 mmol) and DIPEA (92 µL, 0.53 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-N-(2-

sulfamoylpyridin-4-yl)-2-(3-(trifluoromethyl)piperidin-1-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.0014 g, 2.1%; LRMS (ESI): Calcd [M+H]+: 498.1, found: 498.1.

[001008] ^{1}H NMR(400 MHz, $CDCl_3$): δ 11.33 (s, 1H), 8.85 (s, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 3.6, 2.0 Hz, 1H), 7.98 (dd, J = 4.8, 4.0 Hz, 1H), 7.55 (m, 2H), 5.32(s, 2H), 3.88 (d, J = 10.4 Hz, 1H), 3.45 (d, J = 12.0 Hz, 1H), 3.35 (dd, J = 10.8, 2.0 Hz, 1H), 3.04 (m, 1H), 2.69 (m, 1H), 2.17 (m, 1H), 1.96 (m, 1H), 1.68 (m, 2H).

Compound 157

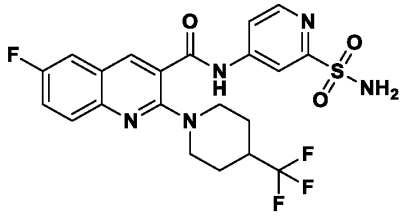
Synthesis of 2-(3,3-difluoropiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide



[001009] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMSO (1 mL) was added 3,3-difluoropiperidine hydrochloride (20 mg, 0.13 mmol) and DIPEA (73 μL, 0.42 mmol). The reaction mixture was heated at 100 ℃ for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(3,3-difluoropiperidin-1-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a beige powder. Yield: 0.013 g, 27%; LRMS (ESI): Calcd [M+H]+: 466.12, found: 466.3.

Compound 158

Synthesis of 6-fluoro-N-(2-sulfamoylpyridin-4-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)quinoline-3-carboxamide



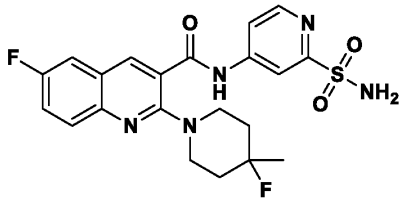
[001010] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMSO (1 mL) was added 4-trifluoromethyl-piperidine hydrochloride (20 mg, 0.13 mmol) and DIPEA (73 μL, 0.42 mmol). The reaction mixture was heated at 100 ℃ for 24 hours. After reaction completion, the reaction mixture was diluted with

water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-N-(2-sulfamoylpyridin-4-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.012 g, 23%; LRMS (ESI): Calcd [M+H]+: 498.12, found: 498.3.

[001011] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.33 (t, J = 4.8 Hz, 1H), 8.27 – 8.15 (m, 2H), 7.66 – 7.57 (m, 2H), 6.41 – 6.35 (m, 2H), 3.66 (s, 2H), 2.84 – 2.74 (m, 2H), 2.08 – 2.03 (m, 1H), 1.76 – 1.71 (m, 2H), 1.56 – 1.41 (m, 2H).

Compound 159

Synthesis of 6-fluoro-2-(4-fluoro-4-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

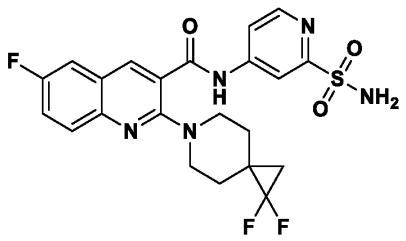


[001012] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMSO (1 mL) was added 4-fluoro-4-methylpiperidine hydrochloride (19 mg, 0.13 mmol) and DIPEA (73 µL, 0.42 mmol). The reaction mixture was heated at 100 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 6-fluoro-2-(4-fluoro-4-methylpiperidin-1-yl)-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.014 g, 29%; LRMS (ESI): Calcd [M+H]+: 462.14, found: 462.1.

[001013] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.47 – 8.40 (m, 1H), 8.35 – 8.27 (m, 1H), 8.22 – 8.13 (m, 1H), 8.07 – 8.02 (m, 1H), 7.80 – 7.74 (m, 1H), 7.74 – 7.68 (m, 2H), 7.63 – 7.55 (m, 1H), 7.20 – 7.15 (m, 1H), 6.45 – 6.38 (m, 1H), 3.42 – 3.35 (m, 2H), 3.12 (t, J = 11.6 Hz, 2H), 1.71 – 1.47 (m, 4H), 1.21 – 1.08 (m, 3H).

Compound 160

Synthesis of 2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

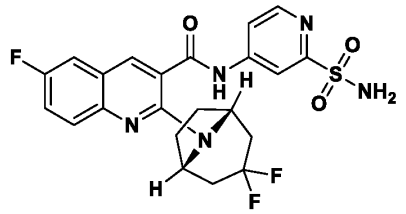


[001014] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMF (1 mL) was added 1,1-difluoro-6-azaspiro[2.5]octane hydrochloride (23 mg, 0.13 mmol) and potassium carbonate (73 mg, 0.525 mmol). The reaction mixture was heated at 75 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.014 g, 29%; LRMS (ESI): Calcd [M+H]+: 492.13, found: 492.3.

[001015] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.35 – 8.27 (m, 1H), 8.21 – 8.12 (m, 2H), 7.66 – 7.61 (m, 1H), 7.60 – 7.56 (m, 1H), 7.20 – 7.15 (m, 2H), 6.44 (s, 2H), 3.26 – 3.22 (m, 2H), 3.18 – 3.10 (m, 2H), 1.62 – 1.37 (m, 2H), 0.93 – 0.86 (m, 2H).

Compound 161

Synthesis of 2-((1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

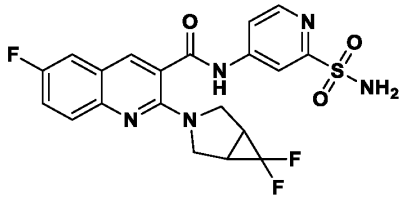


[001016] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMF (1 mL) was added (1S,5R)-3,3-difluoro-8-azabicyclo[3.2.1]octane hydrochloride (23 mg, 0.13 mmol) and potassium carbonate (73 mg, 0.525 mmol). The reaction mixture was heated at 90 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-((1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a an off-white powder. Yield: 0.014 g, 29%; LRMS (ESI): Calcd [M+H]+: 492.13, found: 492.3.

[001017] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.65 (d, J = 5.4 Hz, 1H), 8.45 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.0 Hz, 1H), 7.81 – 7.68 (m, 2H), 7.61 (td, J = 8.9, 3.0 Hz, 1H), 7.47 (s, 2H), 4.58 (s, 2H), 2.34 – 2.26 (m, 2H), 2.24 – 2.15 (m, 2H), 1.92 – 1.88 (m, 4H).

Compound 162

Synthesis of 2-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide

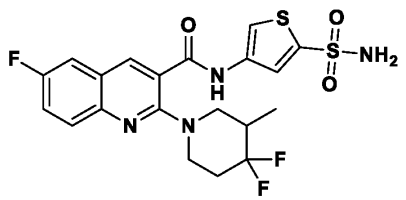


[001018] To a solution of 2-chloro-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide (40 mg, 0.1 mmol) in DMF (1 mL) was added 6,6-difluoro-3-azabicyclo[3.1.0]hexane hydrochloride (20 mg, 0.13 mmol) and potassium carbonate (73 mg, 0.525 mmol). The reaction mixture was heated at 75 °C for 24 hours. After reaction completion, the reaction mixture was diluted with water and MeCN then purified with reversed-phase HPLC to give 2-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)-6-fluoro-N-(2-sulfamoylpyridin-4-yl)quinoline-3-carboxamide as a light yellow powder. Yield: 0.014 g, 29%; LRMS (ESI): Calcd [M+H]+: 464.1, found: 466.3.

[001019] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.65 (d, J = 5.5 Hz, 1H), 8.40 – 8.33 (m, 2H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 7.70 (dd, J = 9.2, 5.2 Hz, 1H), 7.64 (dd, J = 9.1, 3.0 Hz, 1H), 7.56 (td, J = 8.9, 3.0 Hz, 1H), 7.47 (s, 2H), 4.01 (d, J = 11.3 Hz, 2H), 3.86 (dq, J = 11.3, 3.0 Hz, 2H), 2.72 – 2.59 (m, 2H).

Compound 163

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(5-sulfamoylthiophen-3-yl)quinoline-3-carboxamide

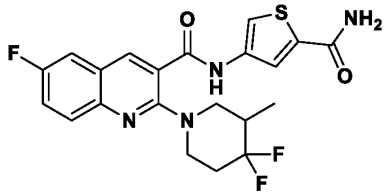


[001020] A mixture of 2-(4,4-difluoro-3-methyl-1-piperidyl)-6-fluoro-3-quinolinecarboxylic acid (0.15 g, 0.46 mmol), HATU (0.26 g, 0.69 mmol), 4-dimethylaminopyridine (0.028 g, 0.23 mmol) in dichloromethane (10 mL) was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated then a solution of 4-amino-2-thiophenesulfonamide (0.1 g, 0.56 mmol) in acetonitrile (10 mL) was added. The reaction mixture was stirred at 80 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, then concentrated. The residue was purified by Prep HPLC obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(5-sulfamoylthiophen-3-yl)quinoline-3-carboxamide as an off-white solid. Yield: 0.050 g, 22%; LRMS (ESI): Calcd [M+H]+: 485.1, found: 485.2.

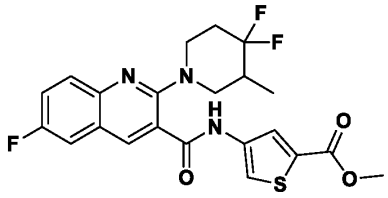
[001021] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 8.41 (s, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.80-7.72 (m 5H), 7.80 (dt, J = 8.8, 2.8 Hz, 1H), 3.89-3.85 (m, 1H), 3.81-3.77 (m, 1H), 3.19 (t, J = 11.2, 1H), 2.96 (t, J = 10.4, 1H), 2.24-2.12 (m, 2H), 2.05-1.91 (m 1H), 0.94 (t, J = 6.8 Hz, 3H).

Compound 164

Synthesis of N-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide

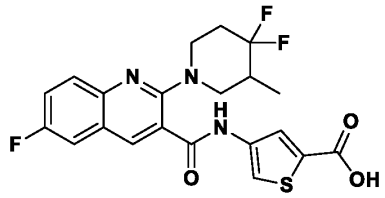


Synthesis of methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate



[001022] A mixture of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid (0.2 g, 0.62 mmol), methyl 4-aminothiophene-2-carboxylate (0.12 g, 0.74 mmol), *N,N*-diisopropylethylamine (0.32 mL, 1.85 mmol) and HATU (0.35 g, 0.93 mmol) in *N,N*-dimethylmethanamide (10 mL) was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 20% ethyl acetate in hexane as an eluent to obtain methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate as an off-white solid.

Synthesis of 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid



[001023] To a stirred solution of methyl 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylate (0.14 g, 0.3 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) was added lithium hydroxide (0.036 g, 1.51 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, then concentrated to afford 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid, which was used in the next step without further purification.

Synthesis of N-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide

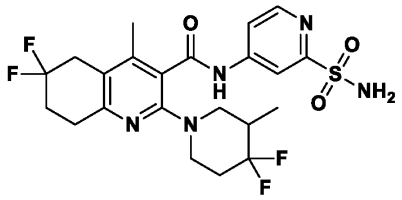
[001024] A mixture of 4-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)thiophene-2-carboxylic acid (0.11 g, 0.25 mmol), the ammonium chloride (0.13 mg, 2.45 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol),

and HATU (0.14 g, 0.37 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 35% ethyl acetate in heptane as an eluent to obtain N-(5-carbamoylthiophen-3-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide an off-white solid. Yield: 0.016 g, 15%; LRMS (ESI): Calcd [M+H]+: 449.13, found: 449.25.

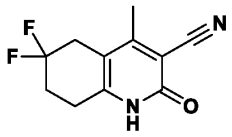
[001025] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.38 (s, 1H), 8.10 (br s, 1H), 7.86 (s, 1H), 7.80-.7.76 (m, 2H), 7.74 (dd, J = 9.2, 2.8 Hz, 1H), 7.59 (dt, J = 8.8, 2.8 Hz, 1H), 7.44 (br s, 1H), 3.19-3.88 (m, 1H), 3.82-3.78 (m, 1H), 3.18 (t, J = 11.2 Hz, 1H), 2.95 (t, J = 10.8 Hz, 1H), 2.32-2.12 (m, 2H), 2.06-1.92 (m 1H), 0.93 (d, J = 6.8 Hz, 3H).

Compound 165

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide



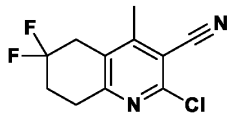
Synthesis of 6,6-difluoro-4-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile



[001026] A mixture of methyl cyanoacetate (4 mL, 37 mmol), acetaldehyde (2.1 mL, 37 mmol) and *L*-proline (0.43 g, 3.7 mmol) was heated at 80 °C for 30 minutes. After reaction completion, the reaction mixture was cooled to room temperature then 4,4-difluorocyclohexanone (5 g, 37 mmol) and ammonium acetate (4.3 g, 56 mmol) were added. The reaction mixture was stirred at 150 °C for 1 hour. After reaction completion, water was added and extracted with ethyl acetate. The combined organic layers were dried over sodium

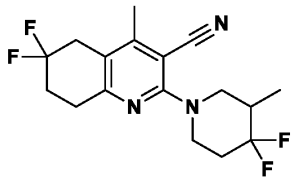
sulfate, filtered, then concentrated to afford 6,6-difluoro-4-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (5.0 g) which was used in the next step without further purification.

Synthesis of 2-chloro-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile



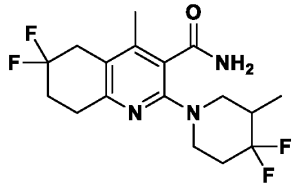
[001027] A suspension of 6,6-difluoro-4-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (5 g, 22 mmol) in phosphoryl trichloride (50 mL) was heated at 100 °C for 4 hours. After reaction completion, excess phosphoryl trichloride was distilled out. The residue was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 30-40% ethyl acetate in heptane to afford 2-chloro-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile as a yellow solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile



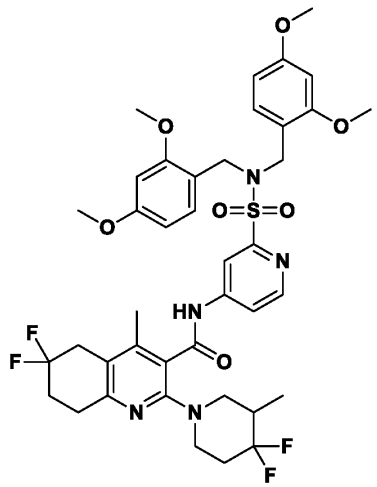
[001028] To a stirred solution of 2-chloro-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (0.5 g, 2.1 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was added *N,N*-diisopropylethylamine (1.8 mL, 10 mmol) dropwise at room temperature. The reaction mixture was cooled to 0 °C and 4,4-difluoro-3-methylpiperidine hydrochloride (0.83 g, 6.2 mmol) was added. The reaction mixture was warmed to room temperature and heated 150 °C for 16 hours. After reaction completion, cold water was added and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 20-25 % ethyl acetate in heptane to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile as a pale yellow solid.

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[001029] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (0.5 g, 1.5 mmol) in dimethyl sulfoxide (10 mL, 140 mmol) was added potassium carbonate (1.01 g, 7.32 mmol) at room temperature. The reaction mixture was cooled to 0 °C and 30% hydrogen peroxide in water (4 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 12 hours. After reaction completion, the reaction mixture was diluted with saturated ammonium chloride solution then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 30-35 % ethyl acetate in heptane to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off-white solid.

Synthesis of N-(2-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide



[001030] A solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.2 g, 0.55 mmol) and bis[(2,4-dimethoxyphenyl)methyl](4-bromo-2-pyridylsulfonyl)amine (0.36 g, 0.67 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate (0.36 g, 1.1 mmol). The reaction mixture was degassed with nitrogen followed by addition RuPhos Pd G3 (0.046 g, 0.06 mmol). The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 25-30% ethyl acetate in hexane to obtain *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off-white solid.

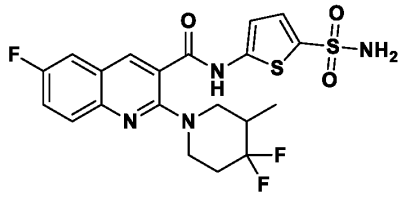
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-*tetrahydroquinoline*-3-carboxamide

[001031] To a solution of *N*-(2-(*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)pyridin-4-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-5,6,7,8-tetrahydroquinoline-3-carboxamide (0.28 g, 0.34 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 hours. After reaction completion, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by reversed-phase HPLC to obtain 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6,6-difluoro-4-methyl-N-(2-sulfamoylpyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carboxamide as an off-white solid. Yield: 0.06 g, 34%; LRMS (ESI): Calcd [M+H]+: 516.17, found: 516.30.

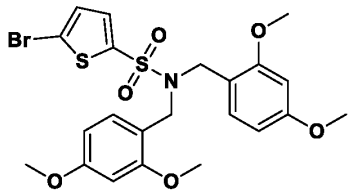
[001032] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1H), 8.61(d, J = 5.2 Hz, 1H), 8.35 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 5.6, 2.0 Hz, 1H), 7.47 (br s, 2H), 3.62-3.58 (m, 1H), 3.52-3.49 (m, 1H), 3.21 (t, J = 15.2 Hz, 2H), 3.06 (t, J = 10.8 Hz, 1H), 2.96 (t, J = 6.4 Hz, 2H), 2.85 (t, J = 9.6 Hz, 1H), 2.34-2.26 (m, 2H), 2.15 (s, 3H), 2.04-1.99 (m, 2H), 1.87-1.75 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H).

Compound 166

Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(5-sulfamoylthiophen-2-yl)quinoline-3-carboxamide

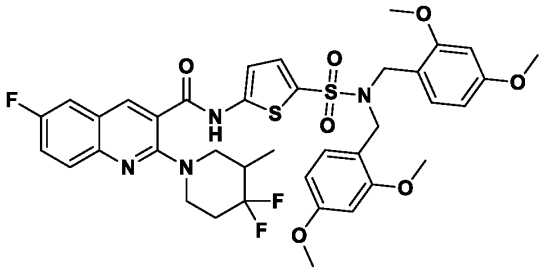


Synthesis of 5-bromo-N,N-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide



[001033] To a stirred solution of bis(2,4-dimethoxybenzyl)amine (1.2 g, 3.8 mmol) and *N,N*-diisopropylethylamine (1.2 g, 9.6 mmol) in dichloromethane (20 mL) was added 5-bromothiophene-2-sulfonyl chloride (0.5 g, 1.9 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by column chromatography using 20-30% ethyl acetate in hexane as an eluent to afford 5-bromo-*N,N*-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide as an off-white solid.

Synthesis of N-(5-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-2-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide



[001034] To a stirred solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fl uoroquinoline-3-carboxamide (0.2 g, 0.62 mmol) and 5-bromo-*N,N*-bis(2,4-dimethoxybenzyl)thiophene-2-sulfonamide (0.4 g, 0.74 mmol) in 1,4-dioxane (10 mL) were added Brettphos Pd G3 (0.056 g, 0.06 mmol) and cesium carbonate (0.6 g, 1.9 mmol). The reaction mixture was heated at 100 °C for 16 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, then concentrated afford *N*-(5-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-2-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide as a white solid, which was used in the next step without further purification.

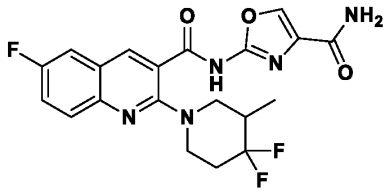
Synthesis of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-N-(5-sulfamoylthiophen-2-yl)quinoline-3-carboxamide

[001035] To a stirred solution of *N*-(5-(*N,N*-bis(2,4-dimethoxybenzyl)sulfamoyl)thiophen-2-yl)-2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide (0.30 g, 0.38 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.8 mL) was added dropwise at 0-5 °C. The reaction mixture was stirred at room temperature for 16 hours. After reaction completion, the reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate, then extracted in ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated. The residue was purified by HPLC to afford 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoro-*N*-(5-sulfamoylthiophen-2-yl)quinoline-3-carboxamide as an off-white solid. Yield: 0.050 g, 27%; LRMS (ESI): Calcd [M+H]+: 485.1, found: 485.2.

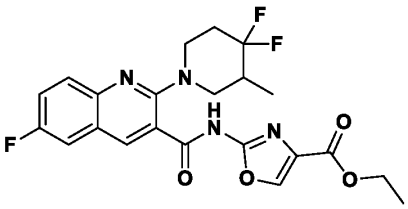
[001036] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H), 8.50 (s, 1H), 7.82-7.74 (m, 2H), 7.63 (dt, J = 8.8, 3.2 Hz, 1H), 7.54 (br s, 2H), 7.39 (d, J = 4.0 Hz, 1H), 6.80 (d, J = 4.0 Hz, 1H), 3.80-3.69 (m, 2H), 3.16 (t, J = 10.4 Hz, 1H), 2.94 (t, J = 10.8 Hz, 1H), 2.25-2.11 (m, 2H), 2.07-1.91 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H).

Compound 167

Synthesis of 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide

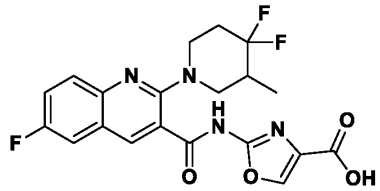


Synthesis of ethyl 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate



[001037] A solution of 2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamide (0.3 g, 0.93 mmol) and ethyl 2-bromooxazole-4-carboxylate (0.25 g, 1.1 mmol) in 1,4-dioxane (15 mL) was added cesium carbonate (0.605 g, 1.86 mmol). The reaction mixture was degassed with nitrogen followed by addition of Xantphos (0.054 g, 0.093 mol) and tris(dibenzylideneacetone)dipalladium (0.085 g, 0.093 mmol). The reaction mixture was heated at 100 °C for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by silica gel column chromatography using 35% ethyl acetate in hexane to obtain ethyl 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate as an off-white solid.

Synthesis of 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid



[001038] To a stirred solution of ethyl 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylate (0.1 g, 0.22 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) was added lithium hydroxide (0.025 g, 1.08 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was concentrated, neutralized with 1N hydrochloric acid, then extracted with ethyl acetate. The combined organic layers were wash with brine, dried over sodium sulfate, filtered, then concentrated to afford 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid, which was used in the next step without further purification.

Synthesis of 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide

[001039] A mixture of 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxylic acid (0.09 g, 0.21 mmol), ammonium chloride (0.11 g, 2.1 mmol) , *N,N*-diisopropylethylamine (0.18 mL, 1 mmol), and HATU (0.12 g, 0.31 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature for 12 hours. After reaction completion, the reaction mixture was diluted with water then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, then concentrated. The residue was purified by prep HPLC to obtain 2-(2-(4,4-difluoro-3-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxamido)oxazole-4-carboxamide as an off-white solid. Yield: 0.015 g, 17%; LRMS (ESI): Calcd [M+H]+: 434.14, found: 434.20.

[001040] ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (s, 1H), 8.47 (s, 1H), 8.44 (br s, 1H), 7.81-7.75 (m, 2H), 7.59 (dt, J = 8.8, 2.8 Hz, 1H), 7.54 (br s, 1H), 7.43 (br s, 1H), 3.76-3.73 (m, 2H), 3.18 (t, J = 10.4 Hz, 1H), 2.94 (t, J = 9.6 Hz, 1H), 2.20-2.14 (m, 2H), 2.07-1.95 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H).

Example 2

Na_V Inhibition Assay

[001041] Electrophysiology experiments were performed on Human Embryonic Kidney 293 cells (HEK) or Chinese hamster ovary cells (CHO) transfected with the full-length cDNA coding for the appropriate human Na_V sodium channel α-subunit Na_V 1.8. Similarly, experiments are performed on Human Embryonic Kidney 293 cells (HEK) or Chinese hamster ovary cells (CHO) transfected with the full-length cDNA coding for the appropriate human Na_V sodium channel α-subunit, including Na_V 1.7, Na_V 1.6, Na_V 1.5, and Na_V 1.4.

[001042] Sodium currents were measured using the patch-clamp technique in the whole-cell configuration with a HEKA EPC 9 amplifier (HEKA Elektronik Dr. Schulze GmbH, Germany) or SyncroPatch 384PE (Nanion Technologies, Livingston, NJ). Currents can also be measured using an IonFlux 16 automated patch clamp system (Fluxion Biosciences, South San Francisco, USA) as previously described by Moran. *See*, Moran O, Picollo A, Conti F (2003) Tonic and phasic guanidinium toxin-block of skeletal muscle Na channels expressed in Mammalian cells, Biophys J 84(5):2999–3006.

[001043] For manual patch-clamp experiments, borosilicate glass micropipettes (Sutter Instruments, Novato, CA) were pulled to a tip diameter yielding a resistance of 1.0–2.0 MΩ in the working solutions. The composition of intracellular solution was (in mM): CsF 125, EGTA 10, HEPES 10, NaCl 10, and the pH was adjusted to 7.2 with CsOH. The composition of extracellular solution was (in mM): NaCl 135, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, and the pH was adjusted to 7.4 with NaOH. For human Na_V 1.8, 0.3 – 1 μM tetrodotoxin (TTX) was added to the extracellular solution to inhibit native TTX-sensitive current. Peak currents were generally between 0.5–20 nA. Lyophilized stock of each test article was stored at -20 °C, solubilized in DMSO (maximum final concentration 1%) and diluted to the desired concentration with the external solution prior to recording. Current measurements were recorded under continuous perfusion, controlled by syringe pump addition.

[001044] The output of the EPC 9 patch-clamp amplifier was filtered with a built-in low-pass, four-pole Bessel filter having a cutoff frequency of 10 kHz and sampled at 20-50 kHz. For both manual and automated recordings, the membrane was kept at a holding potential of between -120 and -80 mV. Pulse stimulation and data acquisition were controlled with the Pulse software (HEKA Elektronik Dr. Schulze GmbH, Germany) or the IonFlux software (Fluxion Biosciences, South San Francisco, USA). All measurements were performed at room

temperature (about 20–22 °C). Recordings were made at least 5 min after establishing the whole-cell and voltage-clamp configuration to allow for stabilization of the voltage-dependent properties of the channels. Currents were elicited by 10-50 ms step depolarizations from a holding potential to a value between -40 and +10 mV. Peak currents after channel activation were recorded. These data were baseline-normalized, plotted against toxin concentration and analyzed in Microsoft Excel software. Data were fit to a four-parameter logistic equation with the Hill slope set to 1 to determine IC_{50} values and expressed as mean.

[001045] For automated patch-clamp experiment cells in culture dishes were washed twice with Hank's Balanced Salt Solution (HBSS) and treated with Accutase™ for approximately 20 minutes. Immediately before use in SP384PE, the cells were washed in HBSS to remove the Accutase™ and re-suspended in HEPES-buffered physiological saline (HB-PS; extracellular solution, composition is indicated on *page 5*). All experiments were performed at ambient temperature. HEPES-buffered intracellular solution for the whole cell recording was loaded into the intracellular compartment of Nanion 384-well Patch Clamp chip (NPC). Extracellular buffer (HB-PS) was loaded into NPC wells (60 μL per well). The cell suspension was pipetted into the wells of the NPC (20 μL per well). After establishment of the whole-cell configuration, membrane currents were recorded using patch clamp amplifiers in SP384PE system. The current recordings were repeated with 0.1 Hz frequency during 3 min as baseline and 5 min after TA application.

[001046] Test article concentrations were applied to naïve cells (n = 4, where n = replicates/ concentration). Each application consisted of addition of 40 μL of 2X concentrated test article solution to the total 80 μL of final volume of the extracellular well of the NPC electrode. Duration of exposure to each compound concentration was five (5) minutes. Vehicle control was applied for five (5) minutes to the cells (32 replicate wells per experiment). To verify the sensitivity the assay to block, positive control was applied for five (5) minutes to the cells (n = 4, where n = the number of replicas per concentration).

[001047] The composition of the extracellular solution was (in mM): NaCl 137, KCl 4.0, $CaCl_2$ 3.8, $MgCl_2$ 1, HEPES 10, Glucose 10, pH adjusted to 7.4 with NaOH. The composition of the intracellular solution was (in mM): CsCl 50, CsF 90, $MgCl_2$ 2, EGTA 5, HEPES 10, pH adjusted to 7.2 with CsOH.

[001048] Block of hNav1.8 channel was measured using a stimulus voltage patterns shown in Figures 1 and 2; voltage potentials are indicated in Tables 2 and 3. The pulse protocol ***A*** was

repeated 3-min before (baseline) and 5-min during test articles addition; stimulation frequency was 0.1 Hz. The pulse protocol ***B*** was applied in presence of test articles, after Protocol ***A***. Peak current amplitudes were measured for test pulses TP1A (tonic inhibition), TP2A (inactivated state inhibition) and TP25B (use-dependent inhibition). Figure 1 depicts voltage protocols for a new test procedure (Protocol A). Figure 2 depicts voltage protocols for a new test procedure (Protocol B).

Table 1. Voltage-protocol parameters for hNav1.x channels protocol A

Channel	Holding Potential (mV)	200 ms Pre-Pulse Potential (PP, mV)	1000 ms Test Pulse 1 Potential (TP1, mV)	20 ms Recovery Pulse Potential (RP, mV)	20 ms Test Pulse 2 Potential (TP2, mV)
Nav1.8	-90	-120	10	-100	10

Table 2. Voltage-protocol parameters for Nav1.x channels – (Protocol B)

Channel	Holding Potential (mV)	20-ms Test Pulse 1 (TP1- TP25; mV)	80-ms Inter Pulse (IP1-IP24; mV)
Nav1.8	-90	10	-90

[001049] Data Analysis: Data acquisition and analyses were performed using the SP384PE system operation software. Data was corrected for leak current. The decrease in current amplitude after test article application was used to calculate the percent block relative to the positive control. Results for each test article concentration ($n \geq 2$) were averaged, the mean and standard deviation values were calculated, and used to generate dose-response curves.

[001050] ***Concentration-response*** data were fit to an equation of the following form: $\% \text{ Block} = (\% 100 / [1 + ([\text{Test}] / IC_{50})^{N}]$,

[001051] where [Test] was the concentration of test article, IC_{50} was the concentration of the test article producing half-maximal inhibition, N was the Hill coefficient and % Block was the percentage of ion channel current inhibited at each concentration of a test article. Nonlinear least squares fits were solved with the XL*fit* add-in for Excel (Microsoft, Redmond, WA).

[001052] Nav1.8 Channel Data Analysis

[001053] *Tonic block* was calculated as:

$$\% \text{ Block (TP1A)} = (1 - I_{TP1A,\ TA} / I_{TP1A,\ Baseline}) \times 100\%,$$

[001054] where $I_{TP1A,\ Baseline}$ and $I_{TP1A,\ TA}$ were the inward peak Na^+ currents elicited by the TP1A in control (baseline) and in the presence of a test article, respectively.

[001055] *Inactivated state block*. We define the inactivation state block as decrease in test pulse (TP2A) current amplitude due to the conditioning depolarizing pulse (TP1A). The inactivation state block was calculated as:

$$\% \text{ Block (TP2A)} = (1 - (I_{TP2,\ TA} / I_{TP2A,\ Baseline}) \times 100\%,$$

[001056] where $I_{TP2A,\ Baseline}$ and $I_{TP2A,\ TA}$ were the inward peak Na^+ currents elicited by the TP2A in control (baseline) and in the presence of a test article, respectively.

[001057] *Use-dependent block* was calculated as:

$$\% \text{ Block (TP25B)} = (1 - (I_{TP25B,\ TA} / I_{TP1A,\ Baseline}) \times 100\%,$$

[001058] where $I_{TP25B,TA}$ and $I_{TP25B,Baseline}$ were the inward peak Na^+ currents elicited by the TP25B in control (baseline) and by the TP25B in the presence of a test article.

[001059] The data were corrected for run-down:

$$\%\text{Block'} = 100\% - ((\%\text{Block} - \%\text{PC}) * (100\% / (\%\text{VC} - \%\text{PC})),$$

[001060] where %VC and %PC are the mean values of the current inhibition with the vehicle and positive controls, respectively.

Table 3 – Na_V Isoform Potency and Selectivity

[001061] For Table 3, Column 1, all data were measured in HEK cells. Column 1 provides IC_{50} data for Na_V 1.8/ β1 as measured using the manual patch-clamp technique in the whole-cell configuration with a HEKA EPC 9 amplifier in units of micromolar (μM). ND means not detectable. NT means not tested. For Table 3, Column 2, all data were measured in CHO cells. Column 2 provides IC_{50} data for tonic block of Na_V 1.8 / β3 (TP1A) as measured using the SyncroPatch 384PE (Nanion Technologies, Livingston, NJ) automated patch clamp system in units of micromolar (μM). ND means not detectable. NT means not tested.

Table 3. Compounds

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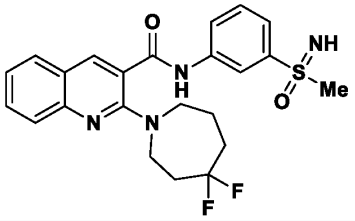
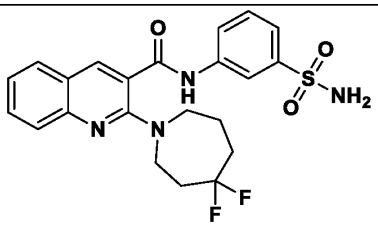
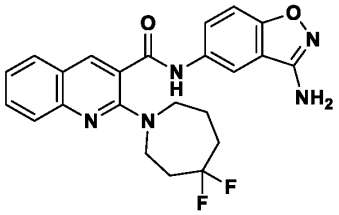
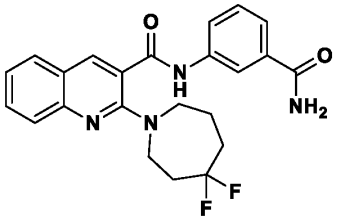
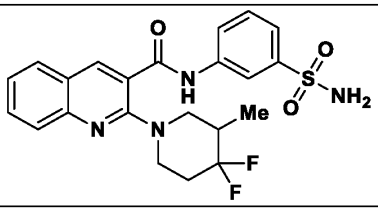
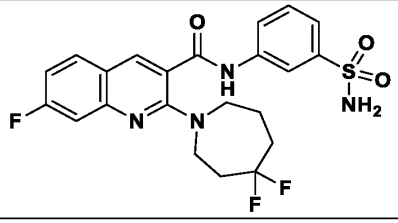
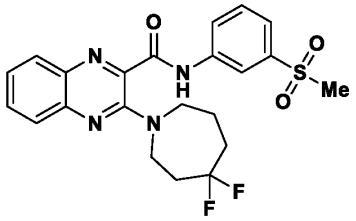
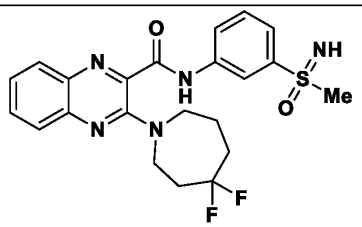
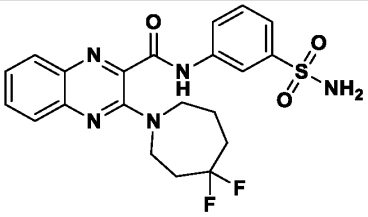
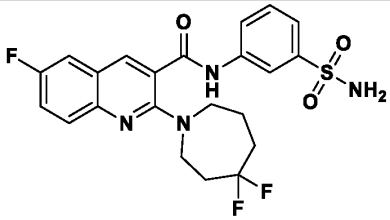
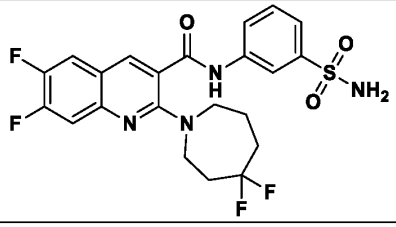
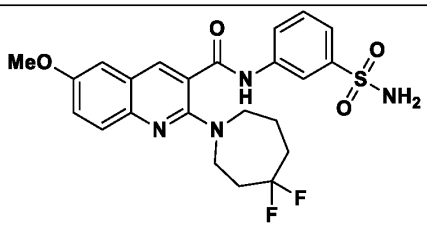
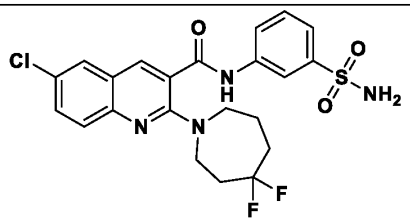
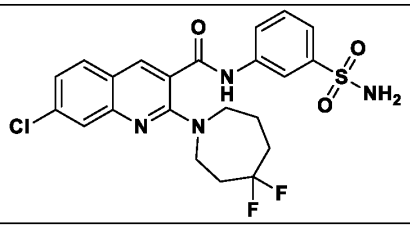
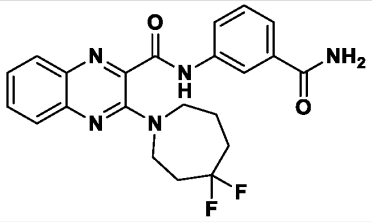
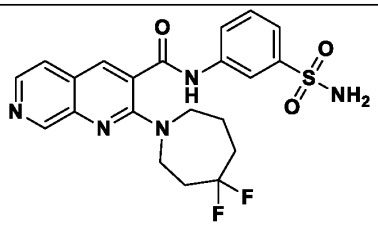
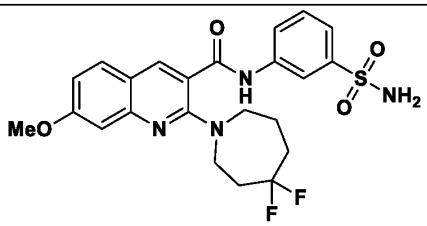
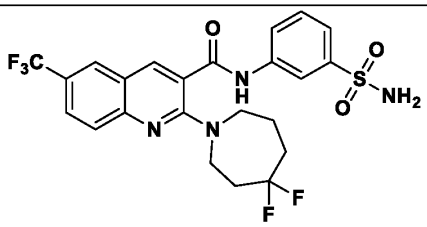
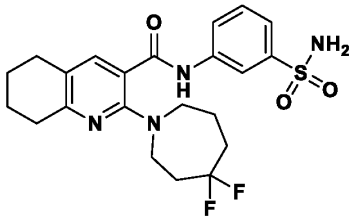
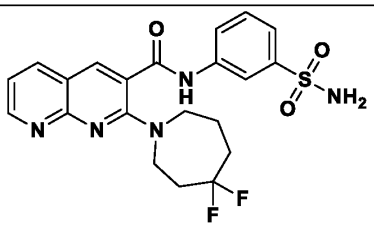
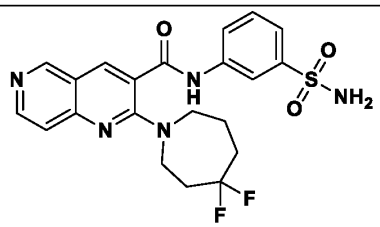
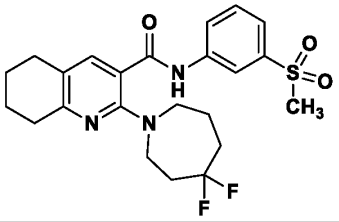
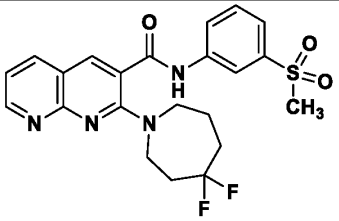
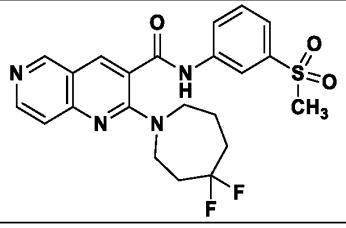
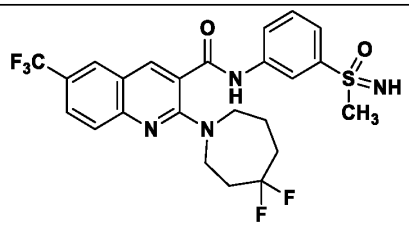
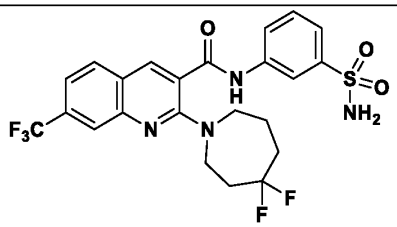
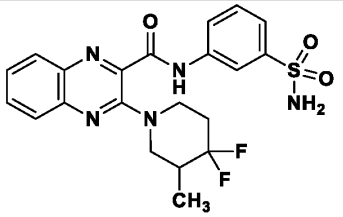
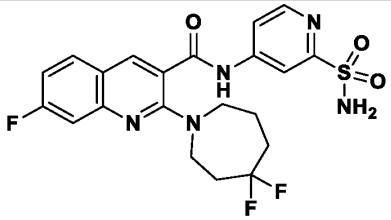
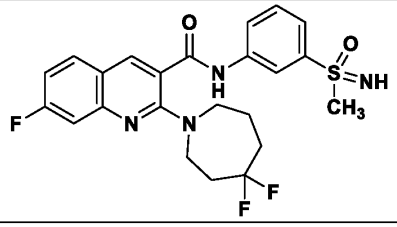
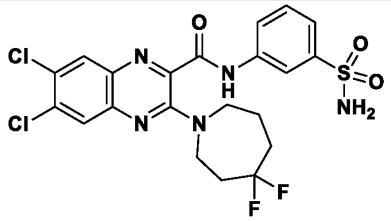
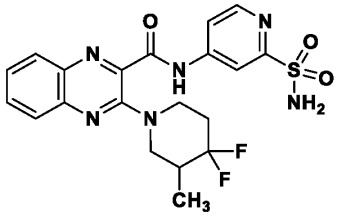
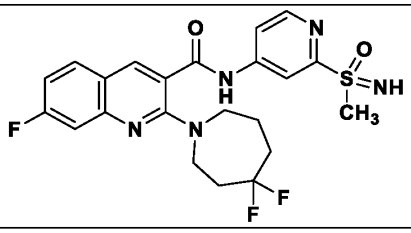
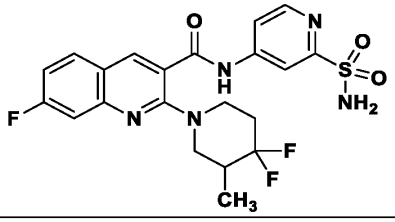
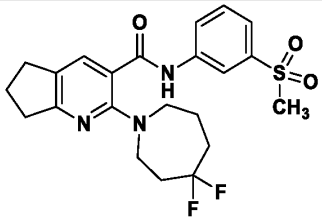
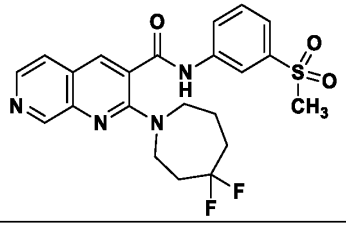
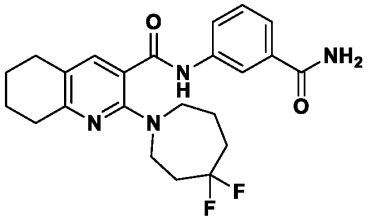
1		0.00060	NT
2		0.0013	NT
3		0.0063	NT
4		0.0032	NT
5		0.0015	NT
6		0.00047	NT

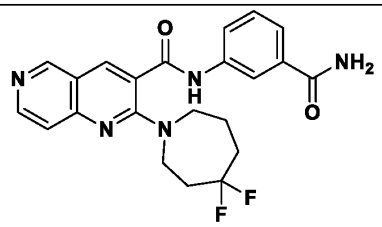
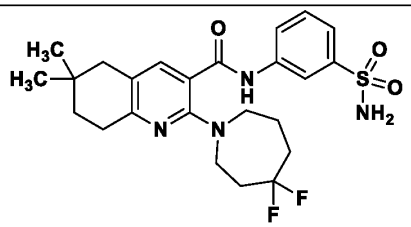
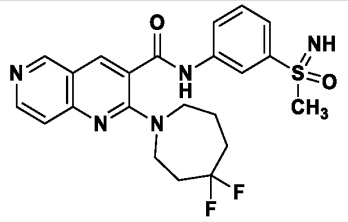
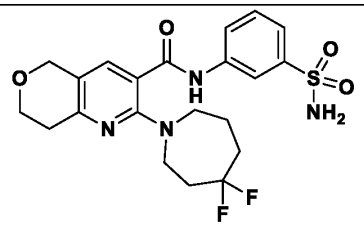
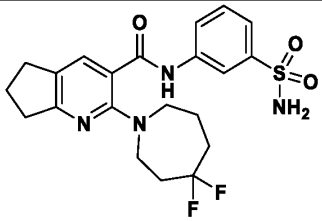
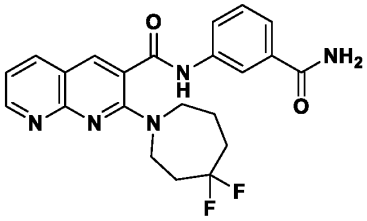
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
7		0.014	NT
8		0.031	NT
9		0.00054	NT
10		0.00038	NT
11		0.00041	NT
12		0.0045	NT

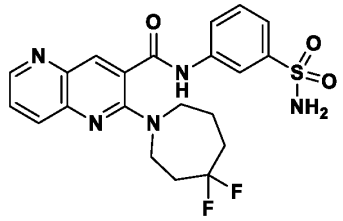
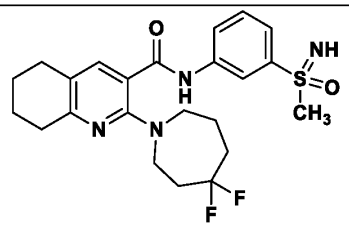
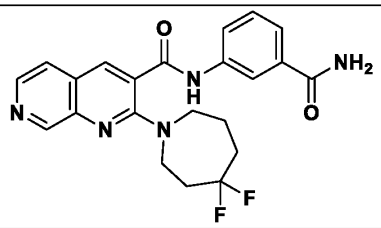
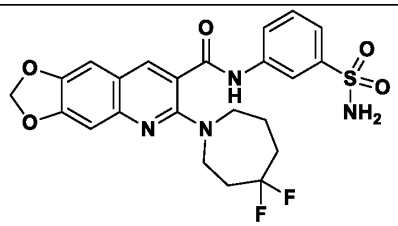
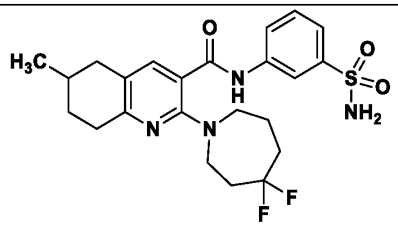
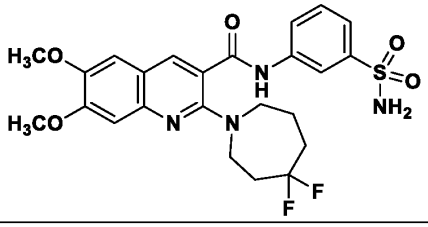
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
13		0.00050	NT
14		0.00046	NT
15		0.047	NT
16		0.016	NT
17		0.00067	NT
18		0.019	NT

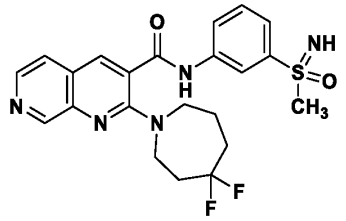
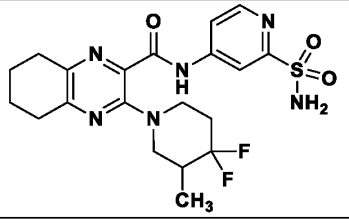
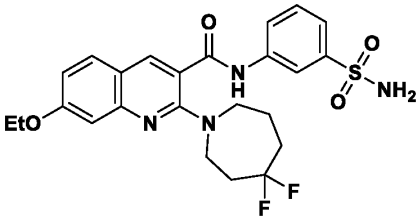
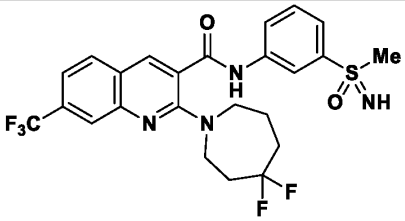
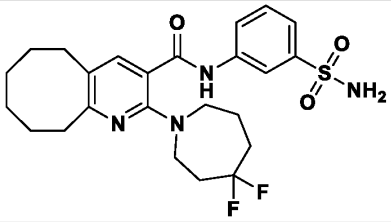
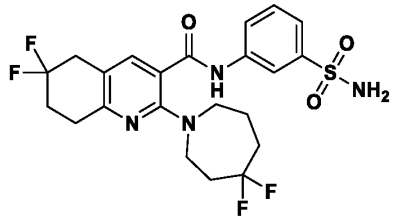
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
19		0.00024	<0.001
20		1.16	NT
21		0.021	NT
22		NT	<0.001
23		NT	>1
24		NT	0.046

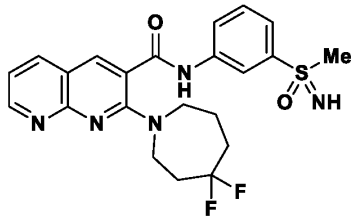
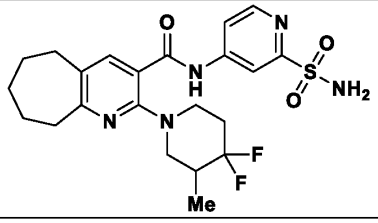
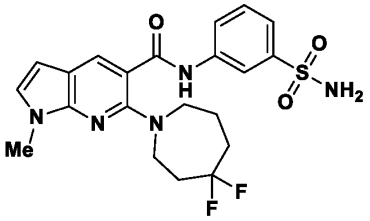
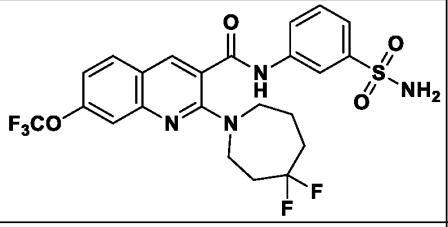
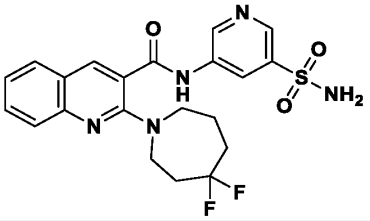
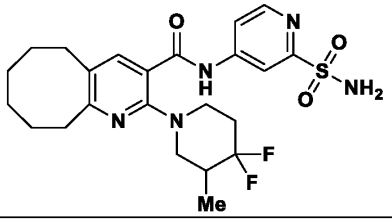
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
25		NT	0.0046
26		NT	0.0048
27		NT	0.012
28		0.00078	NT
29		NT	0.0011
30		NT	0.021

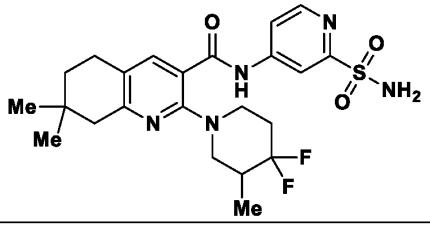
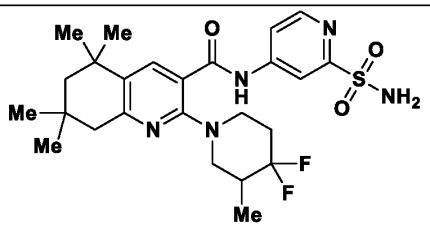
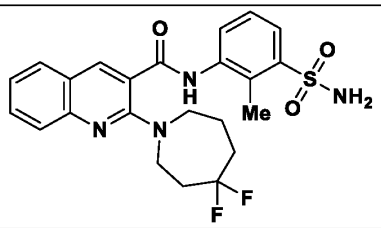
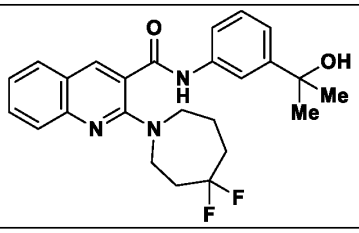
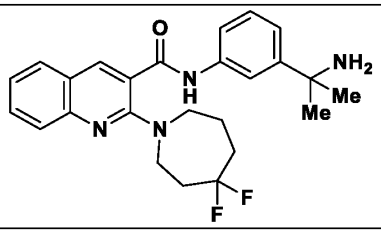
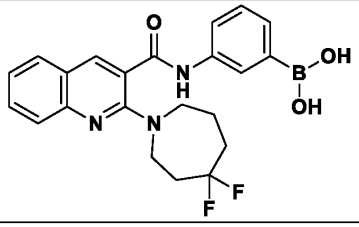
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
31		NT	0.0043
32		0.019	NT
33		0.0022	NT
34		NT	0.0012
35		NT	0.043
36		NT	0.0024

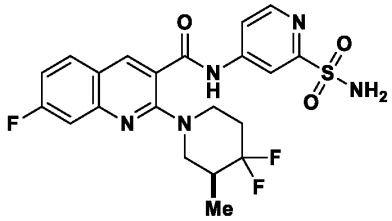
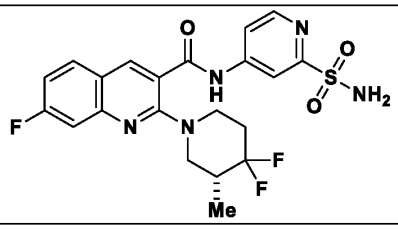
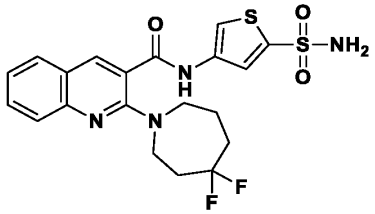
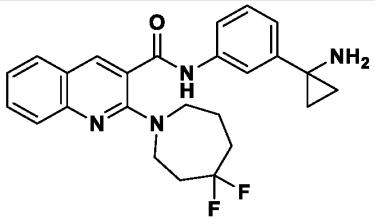
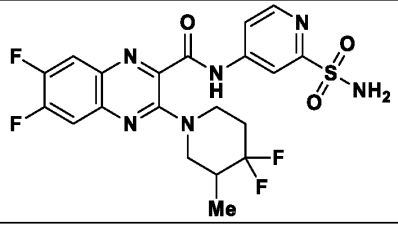
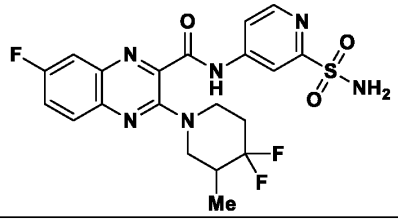
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
37		NT	0.074
38		0.00043	NT
39		NT	0.082
40		0.0092	NT
41		0.0011	NT
42		NT	>1

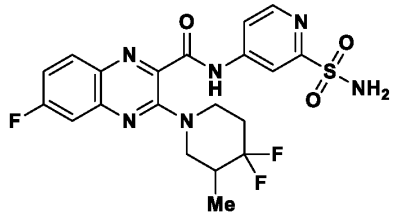
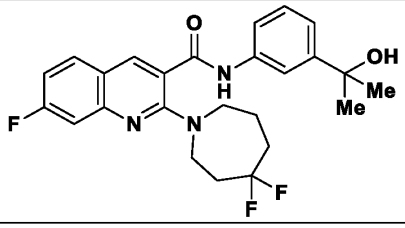
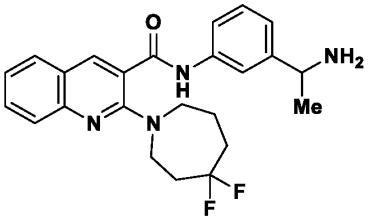
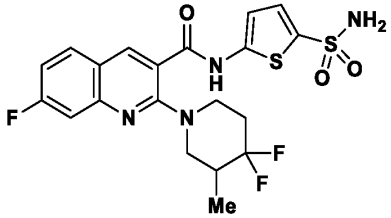
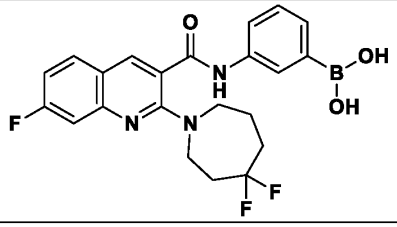
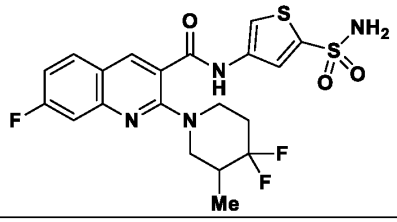
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
43		0.0081	NT
44		NT	0.0007
45		NT	0.167
46		0.10	NT
47		0.0020	NT
48		0.012	NT

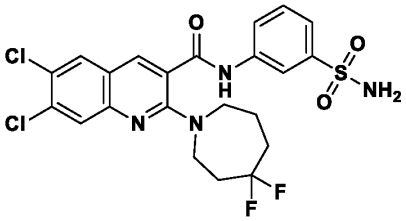
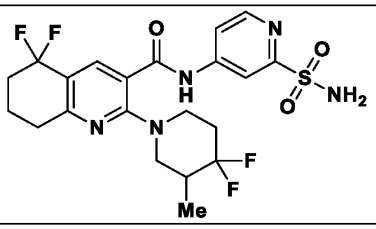
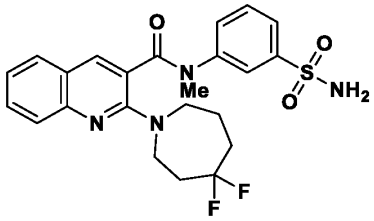
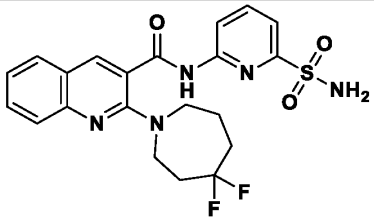
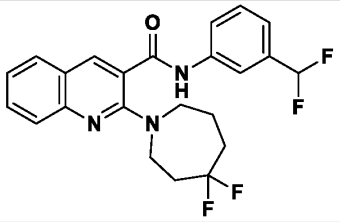
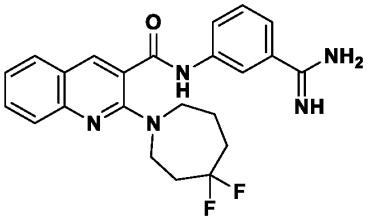
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
49		NT	0.069
51		NT	0.0115
52		NT	0.0012
53		NT	0.0090
55		0.0011	NT
56		0.00060	NT

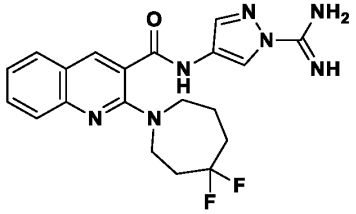
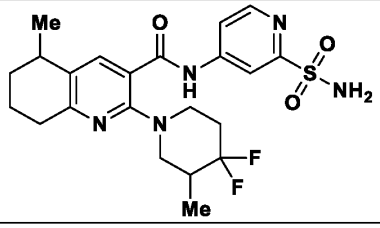
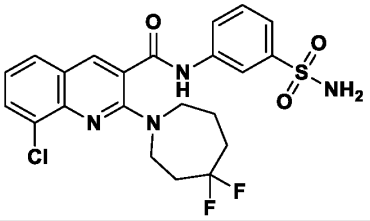
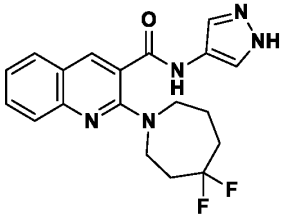
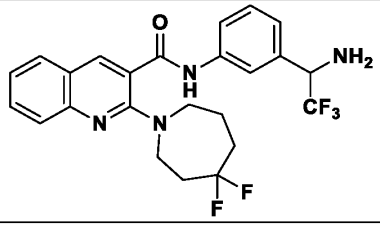
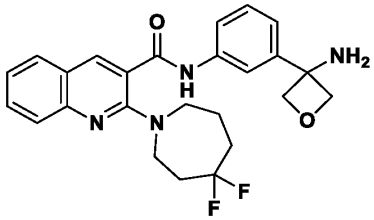
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
57		NT	>1
59		0.0025	NT
60		0.0013	NT
61		0.029	NT
62		0.012	NT
63		0.0022	NT

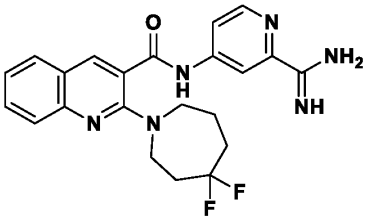
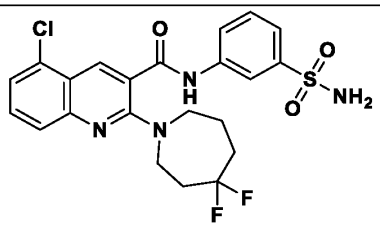
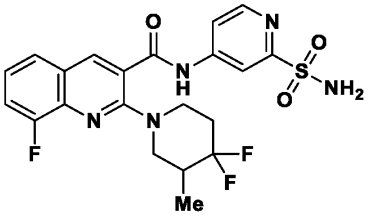
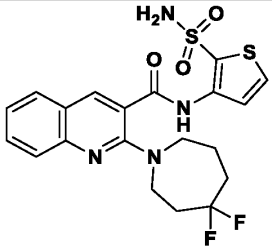
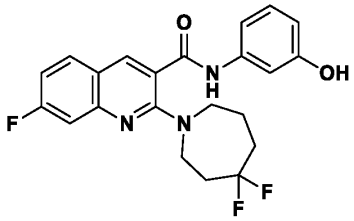
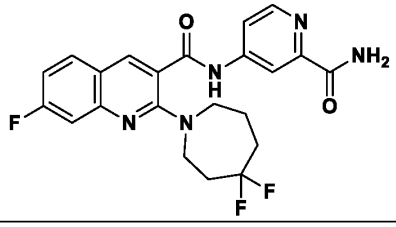
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
64		0.0065	NT
65		0.039	NT
66		0.045	NT
67		0.020	NT
68		0.038	NT
69		0.024	NT

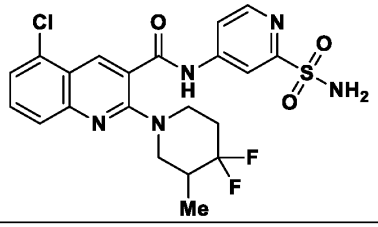
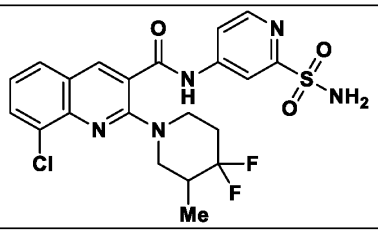
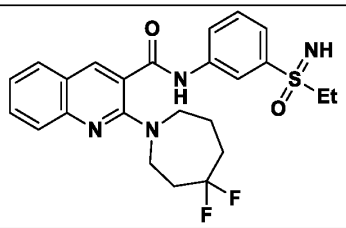
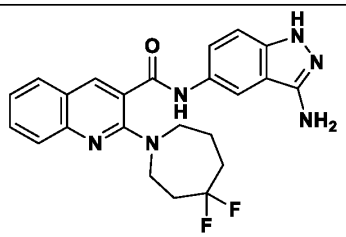
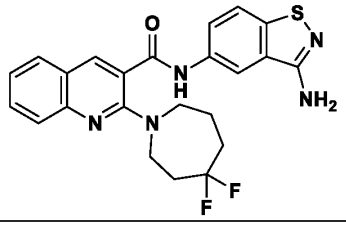
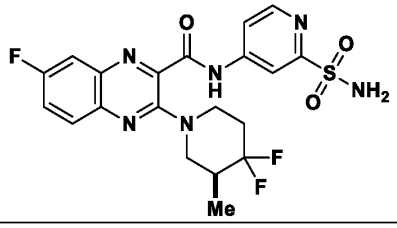
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
70		0.00085	<0.001
71		0.0046	NT
72		0.015	NT
73		0.021	NT
74		0.0075	NT
75		0.0073	NT

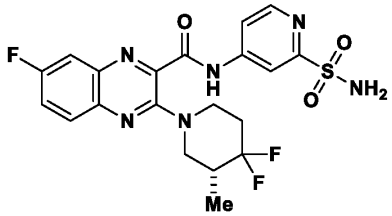
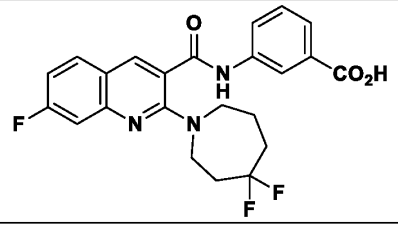
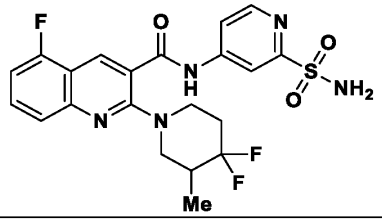
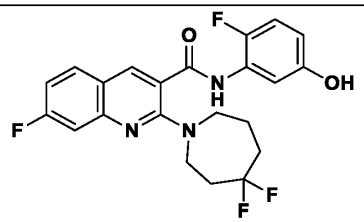
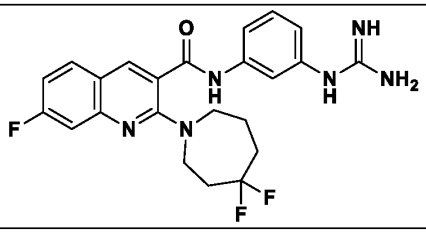
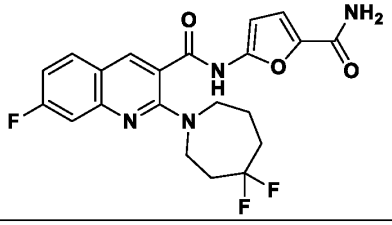
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
76		0.0025	NT
77		0.034	NT
78		NT	0.0311
79		NT	0.0526
80		NT	0.0161
81		NT	0.0026

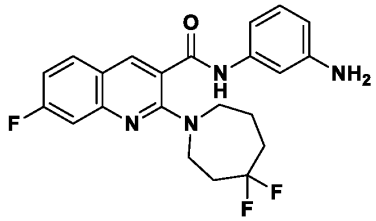
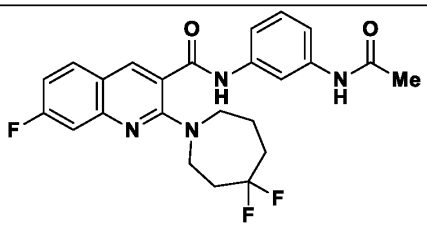
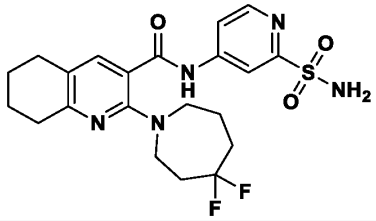
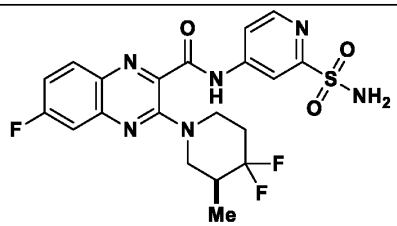
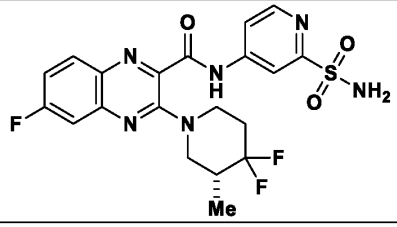
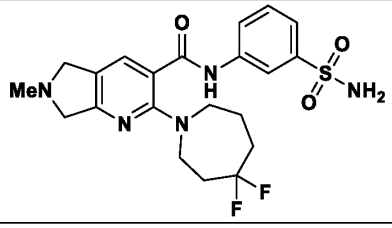
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
82		0.0017	NT
83		0.041	NT
84		0.47	NT
85		NT	0.0069
86		0.51	NT
87		0.0092	0.0009

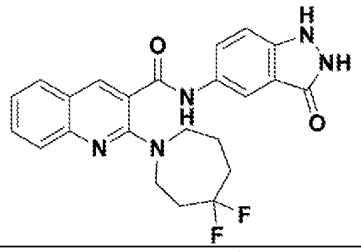
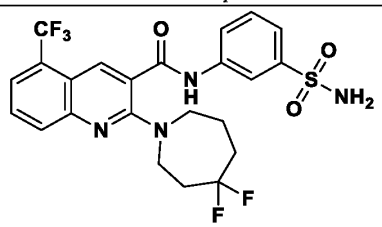
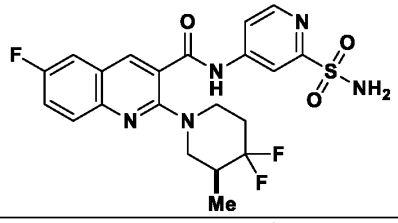
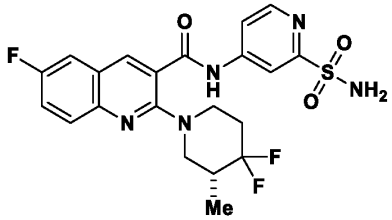
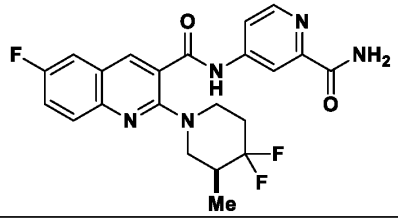
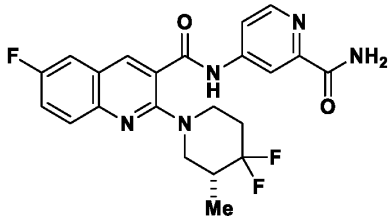
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
88		0.079	0.0155
89		0.0060	NT
90		NT	0.0040
91		NT	0.198
94		NT	0.243
95		NT	0.054

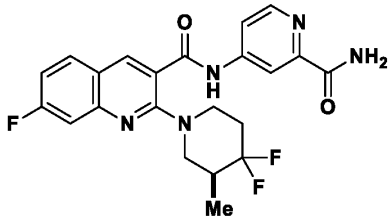
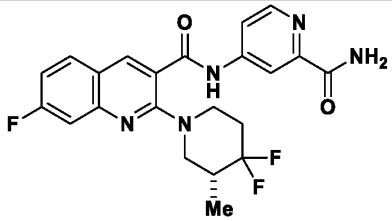
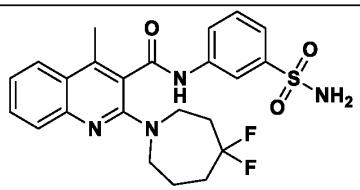
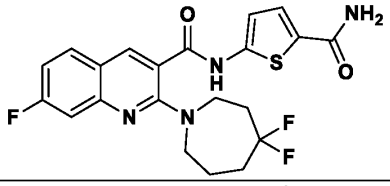
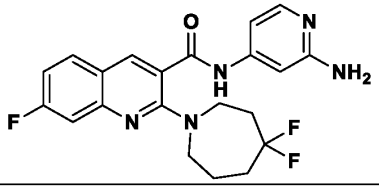
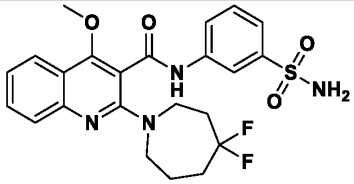
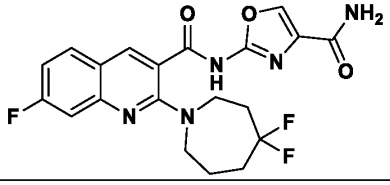
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
96		NT	0.0055
97		NT	0.0031
98		NT	0.0066
99		NT	>1
100		NT	0.028
101		0.0025	NT

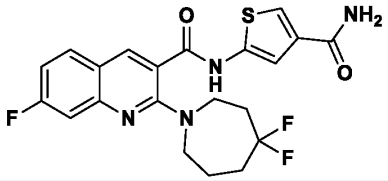
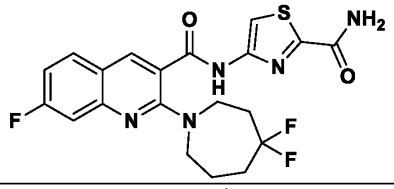
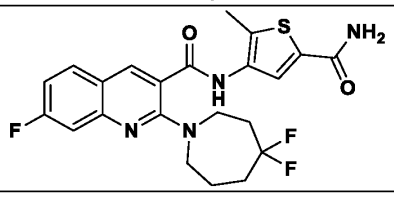
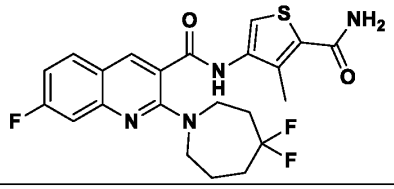
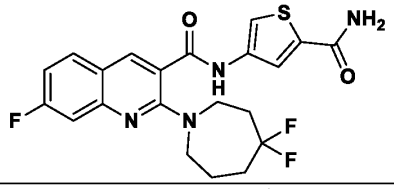
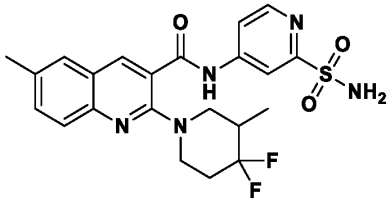
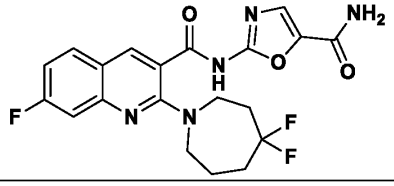
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
102		NT	0.0019
103		NT	0.0044
104		NT	0.0020
105		NT	0.0135
106		NT	0.0684
107		NT	0.0014

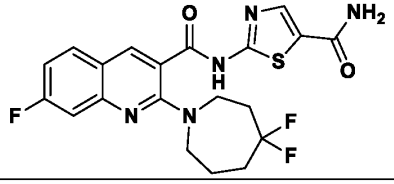
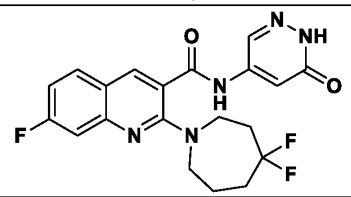
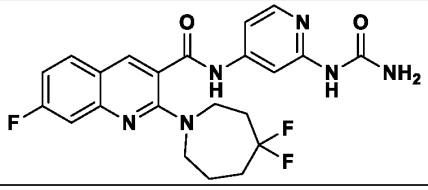
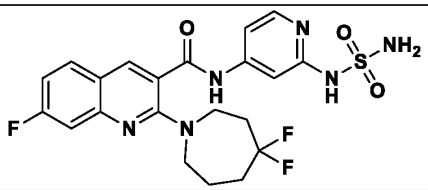
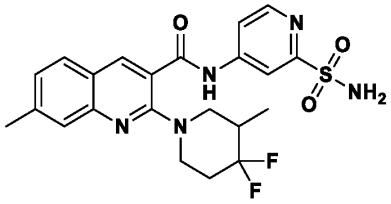
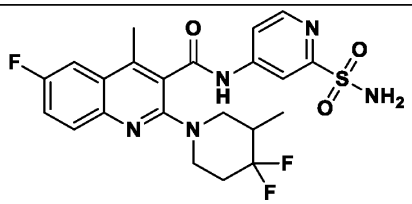
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
108		NT	0.0041
109		NT	0.054
110		NT	0.0015
111		NT	0.497
112		NT	0.0138
113		NT	0.0845

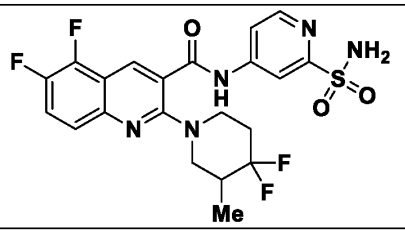
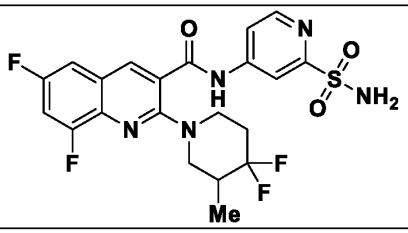
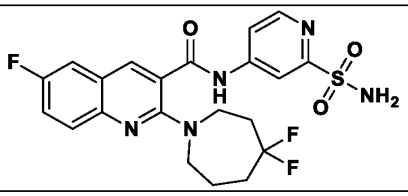
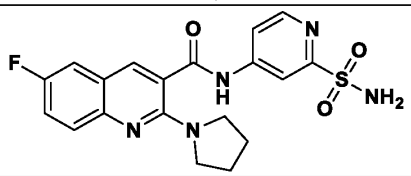
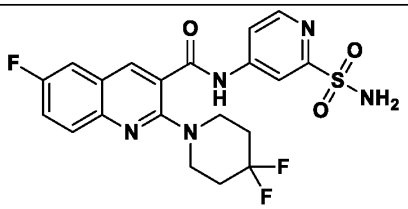
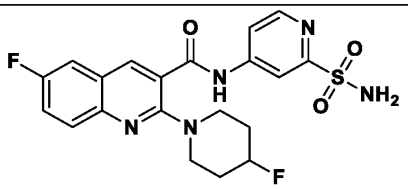
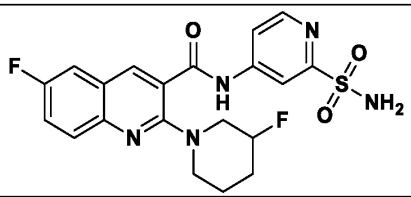
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
114		NT	0.0159
115		NT	0.0498
116		NT	<0.001
117		NT	0.0033
118		NT	0.011
119		2.3	NT

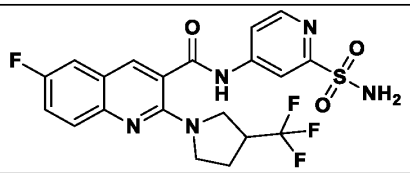
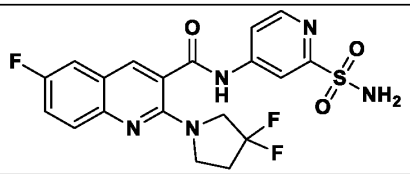
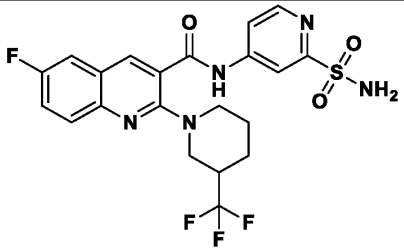
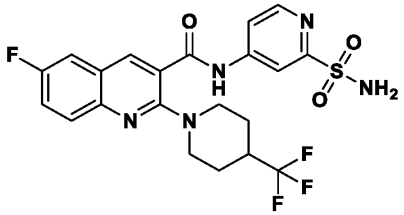
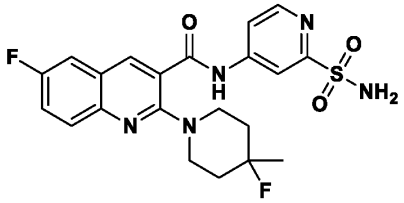
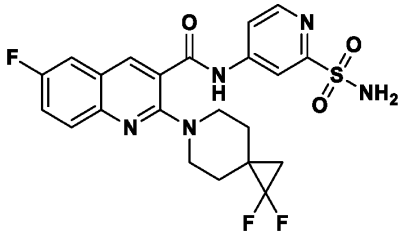
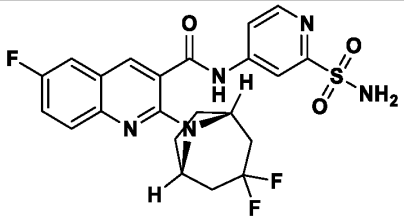
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
120		0.155	NT
121		0.003	NT
122		0.00044	<0.001
123		0.0033	NT
124		0.0050	NT
125		0.011	NT

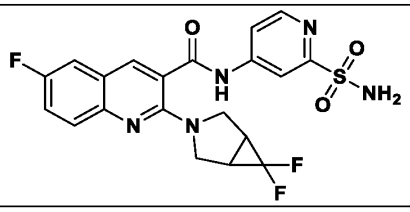
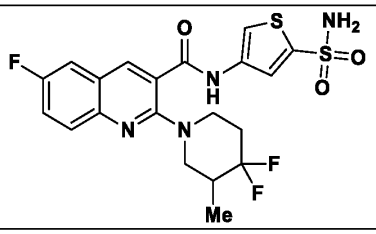
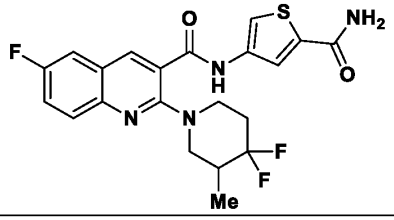
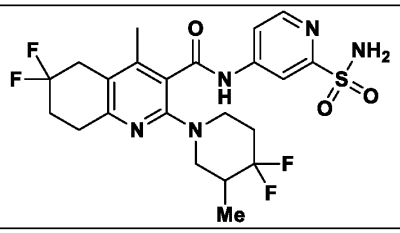
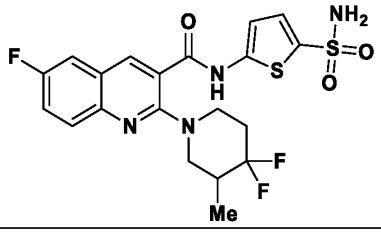
Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
126		NT	0.0114
127		NT	0.019
128		0.00017	NT
129		NT	0.0026
130		NT	0.0052
131		>1	NT
132		NT	0.025

Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
133		NT	0.072
134		NT	0.041
135		NT	0.0088
136		NT	0.0105
137		NT	0.0089
138		NT	0.0036
139		NT	0.556

Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
140		NT	0.244
141		NT	0.147
142		NT	0.0038
143		0.030	0.035
144		0.0012	0.0015
145		NT	0.0023
146		0.00020	NT

Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
147		0.0012	0.0035
148		0.0011	0.0027
149		NT	0.0009
150		NT	>0.1
151		NT	0.0085
152		NT	0.0270
153		NT	>0.1

Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
154		NT	0.0024
155		NT	0.0473
156		NT	0.0227
158		0.0056	NT
159		0.015	NT
160		0.0076	NT
161		0.012	NT

Compound No	Structure	Col. 1 (μM)	Col. 2 (μM)
162		0.018	NT
163		0.0055	NT
164		0.037	NT
165		0.0011	NT
166		0.010	NT

Example 3

Liver Microsome Stability

[001062] Liver microsomes tissue fractions were used for in vitro assessment of metabolic stability of various compounds by cytochrome P450 (CYP) mediated phase I oxidation, and metabolism through other pathways.

[001063] The assay was carried out in 96-well microtiter plates. Compounds were incubated (singlet) at 37 °C in the presence of liver microsomes. Reaction mixtures (25 μL) contained a

final concentration of 1 μM test compound, 0.5 mg/mL liver microsomes protein, 1 mM NADPH, and in 100 mM potassium phosphate, pH 7.4 buffer with 3.3 mM $MgCl_2$. At the end of each time point (0, 15, 30 and 60 min), incubation was stopped by adding quenching solutions (100% acetonitrile, 0.1% formic acid) and samples were transferred to fresh plates for LC/MS/MS analysis.

[001064] The extent of metabolism was calculated as the disappearance of the test article compared to the 0-min control reaction incubations. Verapamil was included as a positive control to verify assay performance. Initial rates are calculated for the compound concentration and used to determine $t_{1/2}$ values and subsequently, the intrinsic clearance, CL_{int} = (0.693)(1/ $t_{1/2}$ (min))(g of liver/kg of body weight)(mL incubation/mg of microsomal protein)(45 mg of microsomal protein/g of liver weight).

Table 4. In vitro stability in liver microsome incubations

	Human		Rat		Cyno	
	$t_{1/2}$ (min)	**CL_{int} (μL/min/mg protein)**	**$t_{1/2}$ (min)**	**CL_{int} (μL/min/mg protein)**	**$t_{1/2}$ (min)**	**CL_{int} (μL/min/mg protein)**
1	79.1	17.5	12.9	107		
2	59.2	23.4	16	86.5		
3	44.3	31.3	22	63.1		
7	>120	<11.6	75.4	18.4		
9	>120	<11.6	69.9	19.8		
10	>120	<11.6	50.5	27.5		
11	>120	<11.6	53.1	26.1		
12	>120	<11.6	33.4	41.5		
13	>120	<11.6	>120	<11.6		
14	>120	<11.6	43.2	32.1		
19	22.4	61.9	13.3	104		
28	>120	<11.6	>120	<11.6		
29	96.9	14.3	50.0	27.7		
31	>120	<11.6	>120	<11.6		
32	50.9	27.2	80.3	17.3		
33	>120	<11.6	>120	<11.6		
38	8.5	120.5	2.5	553		
40	>120	<11.6	45.4	30.6		
41	14.5	95.5	6.8	202.4		
43	>120	<11.6	69.3	20		

	Human		Rat		Cyno	
	$t_{1/2}$ (min)	CL_{int} (µL/min/mg protein)	$t_{1/2}$ (min)	CL_{int} (µL/min/mg protein)	$t_{1/2}$ (min)	CL_{int} (µL/min/mg protein)
48	102.3	16.6	71.2	19.5		
51	87.9	15.8	19.4	71.3		
56	106.1	13.1	89.7	15.5		
60	19.2	72.1	3.9	355.8		
64	30.0	46.2	>120	<11.6		
70	>120	<11.6	>120	<11.6	48.5	28.6
75	>120	<11.6	>120	<11.6		
76	>120	<11.6	>120	<11.6		
80	>120	<11.6	30.4	45.6	18.7	74.2
81	>120	<11.6	54.4	25.5	29.8	46.5
101	>120	<11.6	111	12.5	>120	<11.6
107	>120	<11.6	117.7	11.8	>120	<11.6
108	>120	<11.6	>120	<11.6	>120	<11.6
117	>120	<11.6	>120	<11.6	41.3	33.6
118	>120	<11.6	>120	<11.6	32.4	42.8
122	>120	<11.6	>120	<11.6	>120	<11.6
123	>120	<11.6	>120	<11.6	>120	<11.6
124	>120	<11.6	>120	<11.6	>120	<11.6
125	>120	<11.6	>120	<11.6	>120	<11.6
126/127 1:1 mixture (racemic)	>120	<11.6	>120	<11.6	36.1	38.4

Example 4

Kinetic Solubility

[001065] The kinetic solubility of the test article in pH 7.4 buffer was quantified using its DMSO stock solution. The test article in 10 mM DMSO was diluted with pH 7.4 PBS and mixed by shaking for 1.5 hours followed by vacuum filtration. The sample was then assayed via reverse phase HPLC with UV detection. Quantitation was achieved by the reference to a three-point standard curve constructed via serial dilution of drug substance dissolved in 100% DMSO. Testosterone and amiodarone were used as reference compounds to ensure assay performance. This technique represents a reliable means to achieve a numerical representation of kinetic solubility. However, there may be a slight over-estimation of true solubility due to the presence of 5% DMSO in the final incubation mixes.

Table 5. Kinetic solubility in phosphate buffered saline

Compound	Final [DMSO]	KSol (μM)
1	5.0%	198.1
2	5.0%	248.1
3	5.0%	19.5
70	5.0%	100.5
122	5.0%	94.6
146	5.0%	134.4

Example 5

Pharmacokinetics in Sprague Dawley rat

[001066] Pharmacokinetics (PK) of the test articles were evaluated in male Sprague Dawley rats after single dose administration. Two routes (IV and PO) of administration were evaluated at 0.5 mg/kg and 5.0 mg/kg respectively (n = 3 animals per route). The presence of the test articles in plasma was measured using a fit for purpose LC-MS/MS method and the PK parameters were calculated by Phoenix WinNonlin software. In certain cases, a cassette dosing design was implemented to evaluate the PK of two or more compounds in parallel in a single study.

[001067] The vehicle used in the IV formulation was 1% DMSO, 99% (1:1 propylene glycol / 5% mannitol in water). The vehicle for the PO formulation was 1% DMSO, 99% (0.5% methylcellulose, 0.2% tween 80 (i.e. "MCT"). The IV formulation was given at 1 mL/kg; and the PO formulation was given at 10 mL/kg. Plasma was collected at 0.083, 0.25, 0.5, 1, 2, 4, 8 and 24 h for IV and 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h for PO.

[001068] Each blood collection (about 0.5 mL per time point) was performed from a peripheral vessel from restrained, non-sedated animals of each animal into pre-chilled commercial EDTA-K2 tubes and placed on wet ice until centrifugation. The plasma concentration vs. time profile data is summarized in Table 6. The calculated PK parameters are summarized in Table 7 (IV admin) and Table 8 (PO admin). BLQ = below limit of quantitation.

Table 6. Mean plasma concentration vs time in male Sprague Dawley rats

Compound	Route	Dose (mg/kg)	Time (h)								
			0.083	0.25	0.5	1	2	4	6	8	24
			Mean plasma concentration (ng/mL)								
28	IV	0.5	187	108	74.2	48.6	28.5	15.8		4.94	BLQ
70	IV	0.5	184	145	134	100	79.9	68.3		44.1	10.7
71	IV	0.5	117	96.9	81.4	57.2	54.7	42.6		23.6	7.95

Compound	Route	Dose (mg/kg)	Time (h)								
			0.083	0.25	0.5	1	2	4	6	8	24
			Mean plasma concentration (ng/mL)								
107	IV	0.5	18.3	11.0	9.4	5.87	3.49	BLQ		BLQ	BLQ
108	IV	0.5	23.7	17.3	14.3	12.53	9.64	5.62		3.21	BLQ
122	IV	0.5	169	91.7	93.3	66.3	39.8	18.9		6.46	BLQ
123	IV	0.5	153	116	99.5	69.1	44.5	22.1		6.82	BLQ
124	IV	0.5	119	104	78.5	76.0	56.6	35.1		16.2	BLQ
125	IV	0.5	119	88.7	76.6	70.7	46.6	26.0		11.6	BLQ
28	PO	5.0		211	231	240	167	76.7	25.0	BLQ	BLQ
70	PO	5.0		409	603	765	653	727	530	333	25.4
71	PO	5.0		383	575	622	552	262	218	90.7	20.9
107	PO	5.0		52.5	43.2	33.1	25.7	11.3	6.50	5.44	3.4
108	PO	5.0		136	159	197	171	83.1	41.3	22.3	2.55
122	PO	5.0		813	1006	888	871	489	337	211	18.1
123	PO	5.0		650	793	752	745	313	155	83.1	4.88
124	PO	5.0		672	618	727	649	326	191	110	10.5
125	PO	5.0		494	602	530	410	242	140	95.7	18.6

Table 7. PK parameters in male Sprague Dawley rats (IV dosing)

Compound	Route	Dose (mg/kg)	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	Cl (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
28	IV	0.5	246	220	237	35.4	7.21	2.36
70	IV	0.5	209	1038	1179	8.55	4.63	7.10
71	IV	0.5	133	591	659	20.3	5.80	5.02
107	IV	0.5	23.6	15.2	15.2	402	38.1	1.10
108	IV	0.5	27.8	60.2	67.0	108	36.0	3.91
122	IV	0.5	231	254	276	30.3	5.18	2.32
123	IV	0.5	176	276	299	29.1	4.77	2.19
124	IV	0.5	128	344	423	19.8	5.55	3.37
125	IV	0.5	137	285	337	24.8	6.09	3.07

Table 8. PK parameters in male Sprague Dawley rats (PO dosing)

Compound	Route	Dose	T_{max} (h)	C_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	F (%)
28	PO	5.0	0.50	272	749	802	1.48	33.8
70	PO	5.0	2.33	806	7600	7758	4.28	65.8

Compound	Route	Dose	T_{max} (h)	C_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	F (%)
71	PO	5.0	1.0	622	3548	3723	5.56	56.5
107	PO	5.0	0.25	52.5	156	171	8.10	102
108	PO	5.0	1.0	197	884	927	4.12	147
122	PO	5.0	0.92	1048	5588	5711	4.21	207
123	PO	5.0	1.0	810	3497	3526	3.89	118
124	PO	5.0	0.75	761	3669	3741	4.45	88.5
125	PO	5.0	0.83	628	2920	3134	6.25	93.1

Example 6

Pharmacokinetics in cynomolgus macaque

[001069] Pharmacokinetics (PK) of the test articles were evaluated in male cynomolgus monkeys after single dose administration. Two routes (IV and PO) of administration were evaluated at 0.2 mg/kg and 1.0 mg/kg respectively (n = 3 animals per route). The presence of the test articles in plasma was measured using a fit for purpose LC-MS/MS method and the PK parameters were calculated by Phoenix WinNonlin software. In certain cases, a cassette dosing design was implemented to evaluate the PK of two or more compounds in parallel in a single study.

[001070] The vehicle used in the IV formulation was 1% DMSO, 99% (1:1 propylene glycol / 5% mannitol in water). The vehicle for the PO formulation was 1% DMSO, 99% (0.5% methylcellulose, 0.2% tween 80 (i.e. "MCT"). The IV formulation was given at 1 mL/kg; and the PO formulation was given at 10 mL/kg. Plasma was collected at 0.083, 0.25, 0.5, 1, 2, 4, 8 and 24 h for IV and 0.25, 0.5, 1, 2, 4, 8 and 24 h for PO.

[001071] Each blood collection (about 0.5 mL per time point) was performed from a peripheral vessel from restrained, non-sedated animals of each animal into pre-chilled commercial EDTA-K2 tubes and placed on wet ice until centrifugation. The plasma concentration vs. time profile data is summarized in Table 9. The calculated PK parameters are summarized in Table 10 (IV dosing) and Table 11 (PO dosing). BLQ = below limit of quantitation.

Table 9. Mean plasma concentration vs time in male cynomolgus macaques

Compound	Route	Dose (mg/kg)	Time (h)							
			0.083	0.25	0.5	1	2	4	8	24
			Mean plasma concentration (ng/mL)							
A	IV	0.2	315	117	82.9	63.5	35.7	13.3	2.67	BLQ

Compound	Route	Dose (mg/kg)	Time (h)							
			0.083	0.25	0.5	1	2	4	8	24
			Mean plasma concentration (ng/mL)							
B	IV	0.2	194	105	90.4	88.3	82.0	76.7	52.9	23.3
C	IV	0.2	147	134	115	100	81.6	65.1	40.2	22.8
A	PO	1.0		32.0	198	329	235	69.1	11.9	BLQ
B	PO	1.0		18.6	140	449	552	481	304	72.9
C	PO	1.0		11.7	147	439	447	362	219	89.8

Table 10. PK parameters in male cynomolgus macaques (IV dosing)

Compound	Route	Dose (mg/kg)	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	Cl (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
A	IV	0.2	561	249	255	13.1	1.40	1.56
B	IV	0.2	274	1186	1605	2.28	2.15	11.6
C	IV	0.2	155	1050	1481	2.43	2.34	11.9

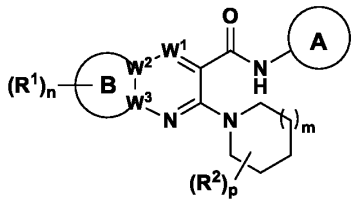
Table 11. PK parameters in male cynomolgus macaques (PO dosing)

Compound	Route	Dose	T_{max} (h)	C_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	F (%)
A	PO	1.0	1.33	350	843	867	1.42	68.0
B	PO	1.0	2.0	552	5826	6631	7.44	98.2
C	PO	1.0	1.67	462	4865	6286	10.2	92.7

[001072] All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference. While the claimed subject matter has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the claimed subject matter is limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

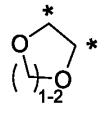
1. A compound of Formula (**I**):



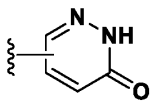
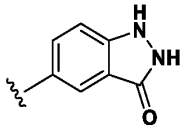
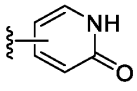
(I)

wherein

$\mathbf{R^1}$, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$;

 optionally substituted with $(R^{3a})_{q1}$;  optionally substituted with $(R^{3a})_{q1}$; or  optionally substituted with $(R^{3a})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C_1-C_6 alkoxy)=;

$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially

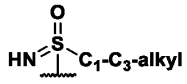
unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

$\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(O)NH_2$, -$NHS(O)_2NH_2$, -$NHC(=NH)NH_2$, -$S(O)_2NH\mathbf{R}$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein $\mathbf{R}$ is hydrogen, C_1-C_3 alkyl, or C_3-C_5cycloalkyl; where the C_3-C_6cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

$\mathbf{m}$ is 0, 1, 2, or 3;

$\mathbf{n}$ is 0, 1, 2, 3, or 4;

$\mathbf{p}$ is 0, 1, 2, 3, 4, 5, or 6;

$\mathbf{q1}$ is 0, 1, or 2; and

$\mathbf{q}$ is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

provided that the compound is not

2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

2-(4,4-difluoroazepan-1-yl)-N-(3-(methylsulfonyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

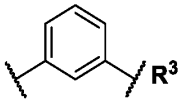
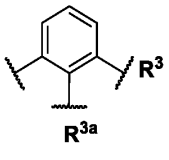
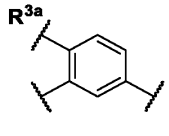
2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

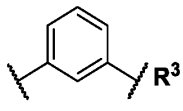
2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof;

or 2-(4,4-difluoroazepan-1-yl)-N-(3-sulfamoylphenyl)-5,6,7,8-tetrahydroquinoline-3-carboxamide or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

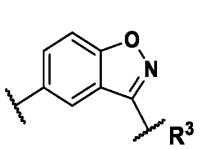
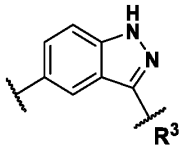
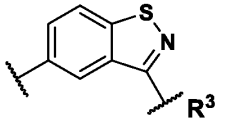
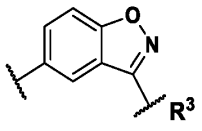
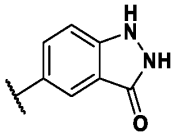
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is C_6-C_{10} aryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, optionally wherein **A** is phenyl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is phenyl substituted with $\mathbf{R^3}$.

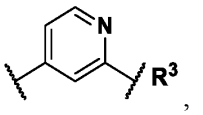
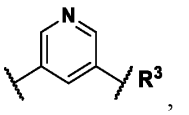
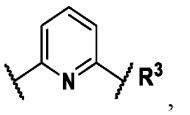
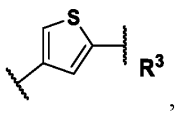
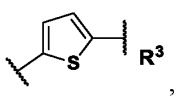
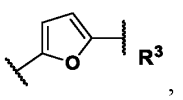
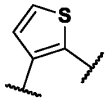
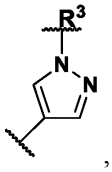
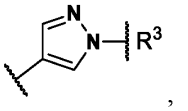
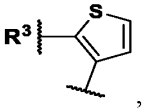
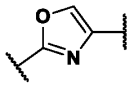
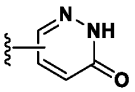
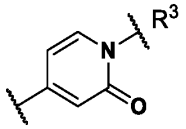
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is , , or , wherein  designates attachment to $\mathbf{R^3}$.

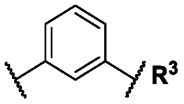
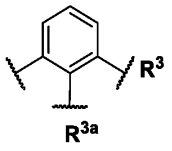
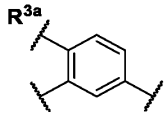
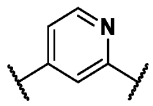
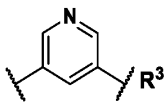
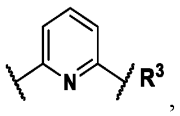
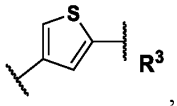
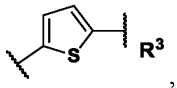
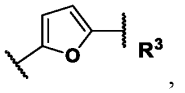
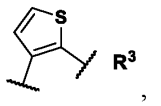
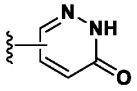
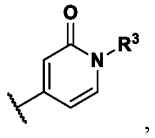
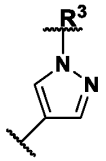
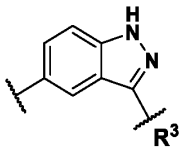
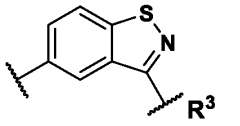
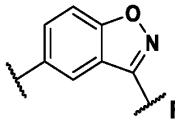
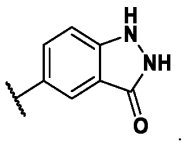
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is , wherein designates attachment to $\mathbf{R^3}$.

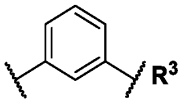
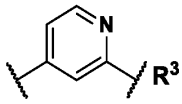
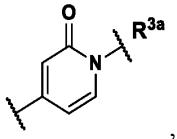
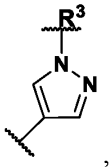
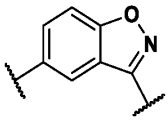
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is 5- to 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or wherein **A** is 9-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or wherein **A** is 10-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$.

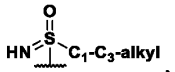
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is , , , , or .

8. The compound of claim 1 or 6, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is 5- or 6-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or wherein **A** is 5-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$, or wherein **A** is 6-membered heteroaryl substituted with $\mathbf{R^3}$ and optionally substituted with $(\mathbf{R^{3a}})_q$.

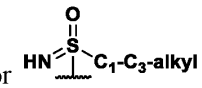
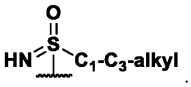
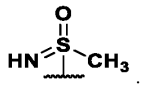
9. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is , , , , , , , , , , , , or .

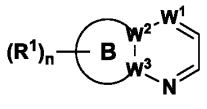
10. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is selected from the group consisting of: , , , , , , , , , , , , , , , , and .

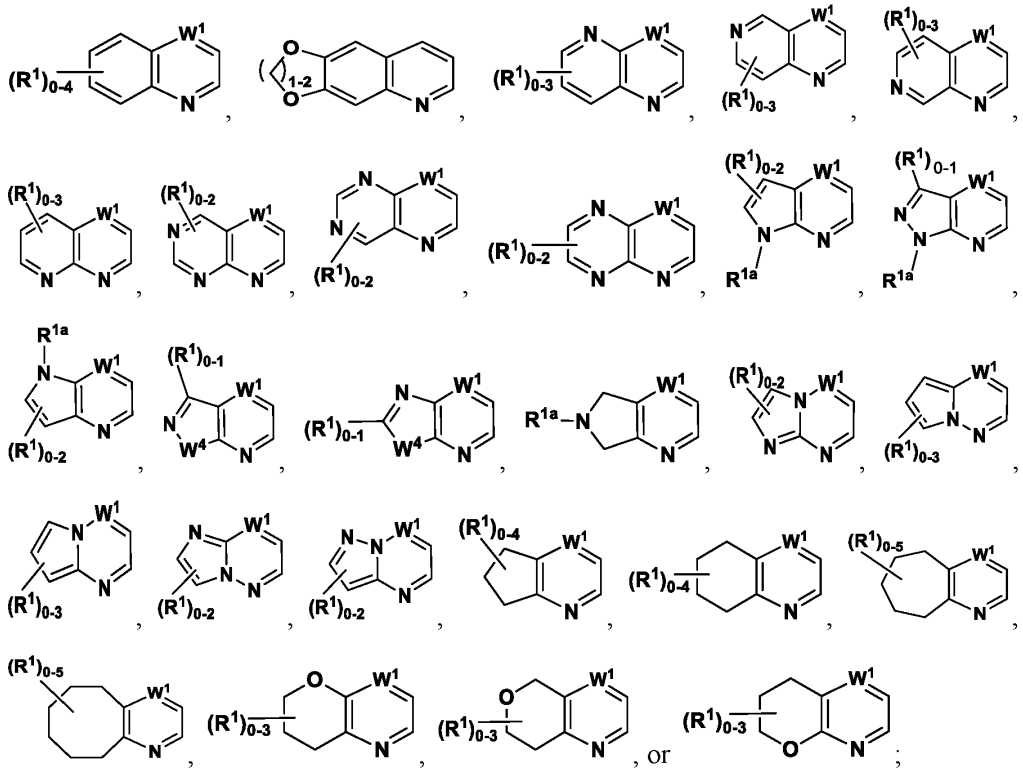
11. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is selected from the group consisting of: , , , , and , wherein  designates attachment to $\mathbf{R^3}$.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is hydrogen, -OH, $-B(OH)_2$, -COOH, hydroxy-C_1-C_3alkyl, $-C(=NH)NH_2$, $-C(O)NH_2$, NH_2, $-NHC(O)C_{1\text{-}3}$alkyl, $-NHC(O)NH_2$, $-NHS(O)_2NH_2$, $-NHC(=NH)NH_2$, $-S(O)_2NH\mathbf{R}$, $-S(O)_2C_1$-C_6-alkyl, amino-C_1-C_3alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl; where the C_3-C_6-cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one $-NH_2$; and

wherein the alkyl in amino-C_1-C_3alkyl is optionally further substituted with 1, 2, 3, or 4 halo.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is -C(O)NH_2, -NH_2, -S(O)$_2$NH**R**, -S(O)$_2$$C_1$-$C_6$-alkyl, or , wherein **R** is hydrogen, C_1-C_3 alkyl or C_3-C_5 cycloalkyl.
14. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof., wherein **A** is pyrazolyl and $\mathbf{R^3}$ is hydrogen.
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is pyridinyl and $\mathbf{R^3}$ is -S(O)$_2$NH**R**, wherein **R** is hydrogen.
16. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **A** is pyridinyl and $\mathbf{R^3}$ is -C(O)NH_2.
17. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is -C(O)NH_2.
18. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof , wherein $\mathbf{R^3}$ is -NH_2.
19. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof , wherein $\mathbf{R^3}$ is -S(O)$_2$NH**R**, optionally wherein **R** is C_1-C_3 alkyl, or optionally wherein **R** is C_3-C_5 cycloalkyl.
20. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is -S(O)$_2$$NH_2$.
21. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is -S(O)$_2$$C_1$-$C_6$-alkyl.
22. The compound of any one of claims 1-13 and 21, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is -S(O)$_2$$CH_3$.
23. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is .
24. The compound of any one of claims 1-13 and 23, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^3}$ is .

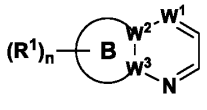
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is

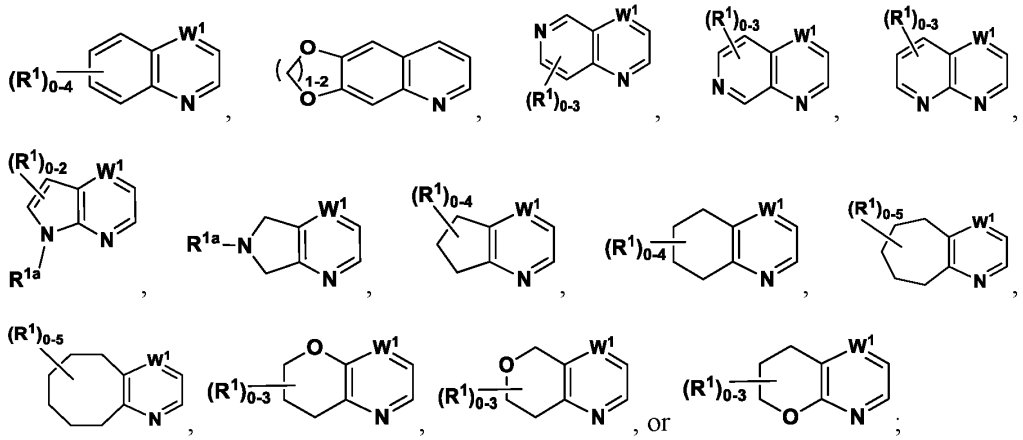


wherein $\mathbf{W^4}$ is O or S;

one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

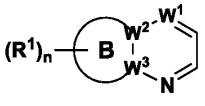
$\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl; or a pharmaceutically acceptable salt thereof and/or an isomer thereof.

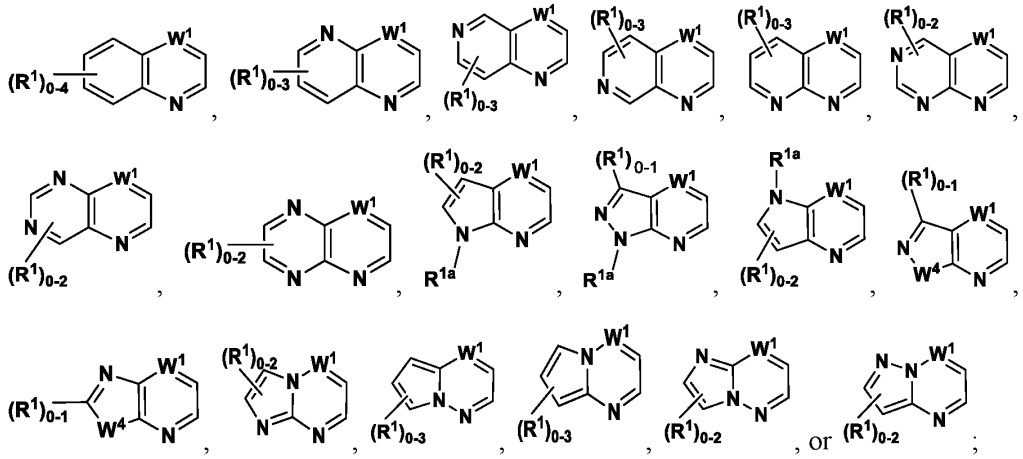
26. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is



one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

$\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl.

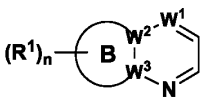
27. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is

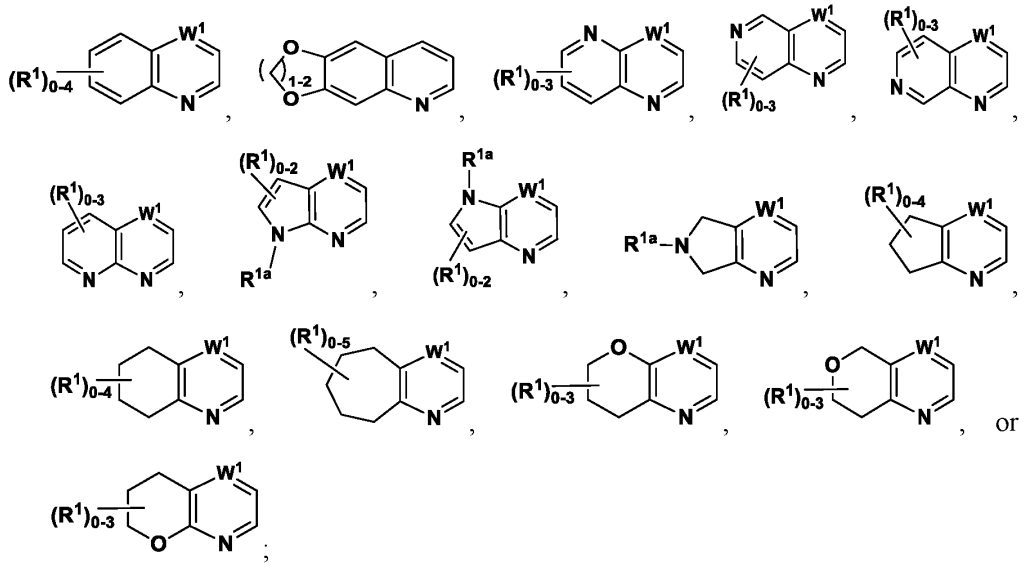


wherein $\mathbf{W^4}$ is O or S;

one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

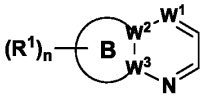
$\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl.

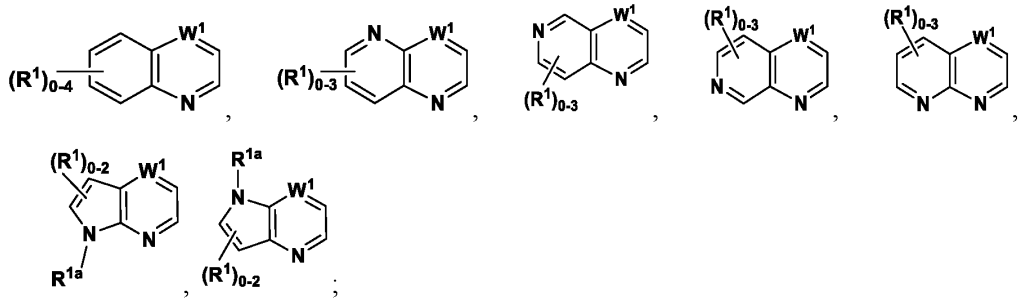
28. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is



one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

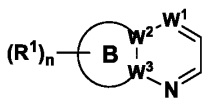
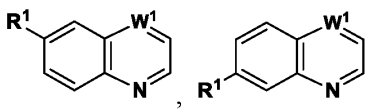
$\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl.

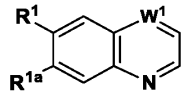
29. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is



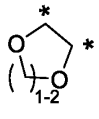
one $\mathbf{R^1}$ can be $\mathbf{R^{1a}}$ as indicated in the above rings; and

$\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl.

30. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein  is ,

or  where $\mathbf{R^{1a}}$ is hydrogen, halogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkylC_1-C_3-alkyl.

31. The compound of any one of claims 27-30, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^{1a}}$ is hydrogen.
32. The compound of any one of claims 27-30, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^{1a}}$ is halogen.
33. The compound of any one of claims 27-30, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^{1a}}$ is C_1-C_6-alkyl.
34. The compound of any one of claims 27-30, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkyl.
35. The compound of any one of claims 27-30, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{R^{1a}}$ is C_3-C_6-cycloalkylC_1-C_3-alkyl.
36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein one $\mathbf{R^1}$ is present and is other than hydrogen.
37. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein two $\mathbf{R^1}$ are present and each is independently other than hydrogen.
38. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein three $\mathbf{R^1}$ are present and each is independently other than hydrogen.
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is C_1-C_6 alkyl, optionally wherein at least one $\mathbf{R^1}$ is -CH_3.
40. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is C_1-C_6 alkoxy, optionally wherein at least one $\mathbf{R^1}$ is -OCH_3.
41. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is C_1-C_6 haloalkyl, optionally wherein at least one $\mathbf{R^1}$ is -CF_3.

42. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is halogen.
43. The compound of any one of claims 1-38 and 42, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is –Cl.
44. The compound of any one of claims 1-38 and 42, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is –F.
45. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^1}$ is halo-C_1-C_6 alkoxy, optionally wherein at least one $\mathbf{R^1}$ is -OCF_3.
46. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein each $\mathbf{R^1}$ is independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy, and halogen.
47. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein each $\mathbf{R^1}$ is hydrogen.
48. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl.
49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein one $\mathbf{R^2}$ is present and is other than hydrogen.
50. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein two $\mathbf{R^2}$ are present and each is independently other than hydrogen.
51. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein three $\mathbf{R^2}$ are present and each is independently other than hydrogen.

52. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^2}$ is halogen.
53. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^2}$ is –F.
54. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^2}$ is C_1-C_6 alkyl.
55. The compound of any one of claims 1-51 and 54, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein at least one $\mathbf{R^2}$ is -CH_3.
56. The compound of any one of claims 1-48, 50, and 51, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl; or wherein two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6 alkyl.
57. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein each $\mathbf{R^2}$ is independently selected from C_1-C_6 alkyl and halogen.
58. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein each $\mathbf{R^2}$ is hydrogen.
59. The compound of any one of claims 1-58, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **m** is 1 or 2.
60. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein **m** is 2.
61. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{W^1}$ is -N=.
62. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{W^1}$ is -C(H)=.

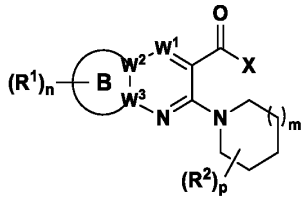
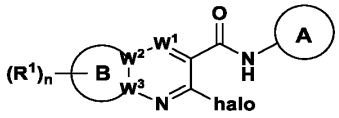
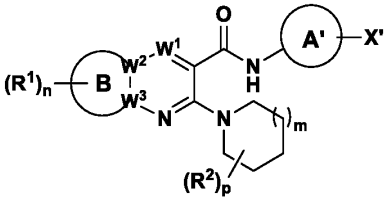
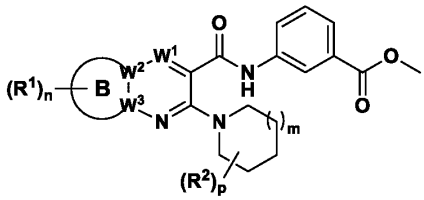
63. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{W^1}$ is -C(C_1-C_6 alkyl)=.
64. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, wherein $\mathbf{W^1}$ is -C(C_1-C_6 alkoxy)=.
65. The compound of claim 1, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, selected from the group consisting of the compounds provided in Table A.
66. A pharmaceutical composition comprising the compound of any one of claims 1-65, or a pharmaceutically acceptable salt thereof and/or an isomer thereof, and a pharmaceutically acceptable carrier.
67. The pharmaceutical composition of claim 66, wherein the composition is an oral or injectable composition, optionally wherein the injectable composition is a subcutaneously injectable composition.
68. A method for the treatment of a condition associated with voltage-gated sodium channel function, including $Na_V1.8$, in a subject, comprising the administration of a therapeutically or prophylactically effective amount of the compound of any one of claims 1-65 or the pharmaceutical composition of any one of claims 66-67.
69. The method of claim 68, wherein the subject is a human.
70. The method of claim 68 or 69, wherein the condition is pain or wherein the condition is associated with pain.
71. The method of claim 68 or 69, wherein the condition is pain.
72. The method of claim 68 or 69, wherein the condition is associated with pain.
73. The method of any one of claims 68-72, wherein the condition is selected from the group consisting of pain associated with erythromelalgia, pain associated with diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, pain associated with trigeminal neuralgia, pain associated with multiple sclerosis, pain associated with arthritis (including osteoarthritis), pain associated with postherpetic neuralgia, cancer pain, pain associated with cluster headache, pain associated with migraine, pain associated with sciatica, pain associated with endometriosis, pain associated with fibromyalgia, postsurgical pain, subacute pain, chronic pain, pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, pain associated with

ocular surgery, pain associated with epilepsy, pain associated with Parkinson's disease, a mood disorder, psychosis, pain associated with amyotropic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

74. The method of claim 68 or 69, wherein the condition is selected from the group consisting of acute pain, subacute pain, post-surgical pain, and ocular pain.

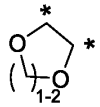
75. A method of inhibiting $NA_v1.8$ comprising contacting $NA_v1.8$ with a compound of any one of claims 1-65.

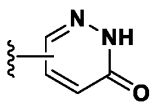
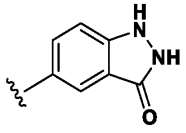
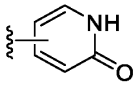
76. A compound, or a salt thereof and/or an isomer thereof, according to any one of the following formulas:

<table>
<tr>
<td>
(A)
where X is OH, OCH_3, OCH_2CH_3, or NH_2;</td>
<td>
(B);</td>
</tr>
<tr>
<td>
(C)
where X′ is SCH_3 or $S(O)CH_3$; and A′ is phenyl or pyridinyl; and</td>
<td>
(D);</td>
</tr>
</table>

wherein

R^1, independently in each instance, is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl; or

two $\mathbf{R^1}$ are attached on adjacent ring carbons in , and together with the adjacent carbons to which they are attached form , where * indicate the shared carbons in  and any remaining $\mathbf{R^1}$ are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, halo-C_1-C_6 alkoxy, C_3-C_6-cycloalkyl, and C_3-C_6-cycloalkylC_1-C_3-alkyl;

A is C_6-C_{10} aryl substituted with R^3 and optionally substituted with $(R^{3a})_q$; 5- to 10-membered heteroaryl substituted with R^3 and optionally substituted with $(R^{3a})_q$;  optionally substituted with $(R^{3a})_{q1}$;  optionally substituted with $(R^{3a})_{q1}$; or  optionally substituted with $(R^{3a})_{q1}$;

$\mathbf{W^1}$ is -N=, -C(H)=, -C(halogen)=, -C(C_1-C_6 alkyl)=, -C(cyclopropyl)=, or -C(C_1-C_6 alkoxy)=;

$\mathbf{W^2}$ and $\mathbf{W^3}$ are each -C-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a double bond, and  is a partially unsaturated 5 to 8-membered carbocyclic ring, a benzo ring, a partially unsaturated 5 to 7-membered heterocyclic ring, or a 5 or 6-membered heteroaromatic ring; or

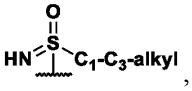
one of $\mathbf{W^2}$ and $\mathbf{W^3}$ is -C- and the other is -N-, the dashed bond between $\mathbf{W^2}$ and $\mathbf{W^3}$ is a single bond, and  is a 5 or 6-membered heterocyclic ring optionally comprising an additional N and where the remaining ring atoms are C;

$\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl; or

two $\mathbf{R^2}$ are attached on adjacent carbons and together with the carbons to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and

C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl; or

two $\mathbf{R^2}$ are attached on the same carbon and together with the carbon to which they are attached form a 3- to 7-membered carbocyclic ring which ring is optionally substituted with 1, 2, or 3 groups independently selected from halogen and C_1-C_6alkyl; and the remaining $\mathbf{R^2}$, independently in each instance, is hydrogen, halogen, or C_1-C_6alkyl;

$\mathbf{R^3}$ is hydrogen, -OH, -$B(OH)_2$, -COOH, hydroxyalkyl, -$C(=NH)NH_2$, -$C(O)NH_2$, -NH_2, -$NHC(O)C_{1\text{-}3}$alkyl, -$NHC(O)NH_2$, -$NHS(O)_2NH_2$, -$NHC(=NH)NH_2$, -$S(O)_2NH\mathbf{R}$, -$S(O)_2C_1$-C_6-alkyl, amino-C_1-C_6alkyl, halo-C_1-C_3alkyl, C_3-C_6-cycloalkyl, 3- to 6-membered heterocycloalkyl, or 

, wherein $\mathbf{R}$ is hydrogen, C_1-C_3 alkyl, or C_3-C_5cycloalkyl; where the C_3-C_6cycloalkyl and the 3- to 6-membered heterocycloalkyl are optionally substituted with one -NH_2; and wherein the alkyl in amino-C_1-C_6alkyl is optionally further substituted with 1, 2, 3, or 4 halo;

$\mathbf{R^{3a}}$, independently in each instance, is hydrogen, halogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, 3, 4, 5, or 6;

q1 is 0, 1, or 2; and

q is 0, 1, 2, or 3.