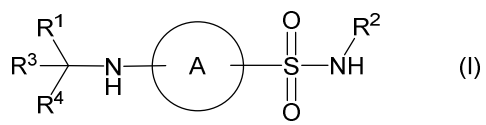


invention provides methods to meet these critical needs.

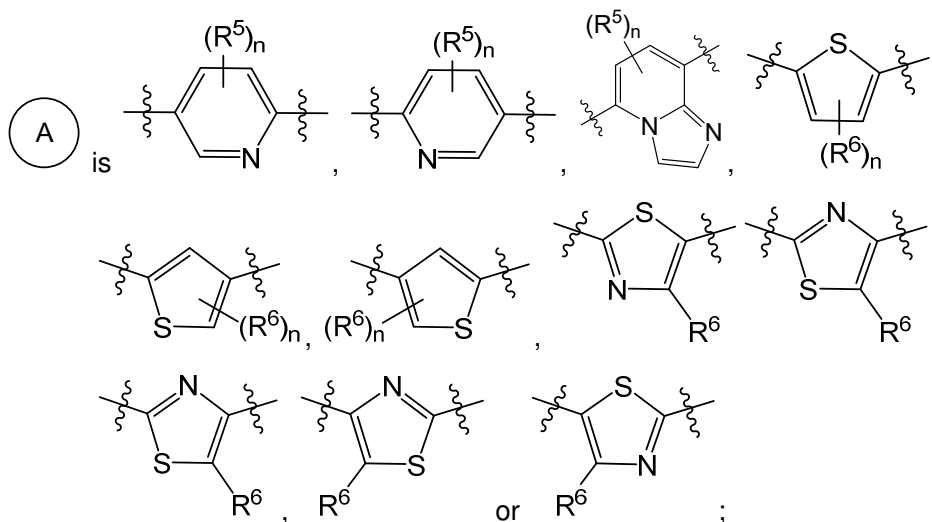
SUMMARY OF THE INVENTION

The present inventiondisclosure is directed to heteroaryl-substituted sulfonamide compounds and pharmaceutical compositions comprising the compounds and methods of using the compounds and the pharmaceutical compositions of the inventiondisclosure for the treatment of diseases or conditions associated with the activity of voltage-gated sodium channels, particularly, $\text{Na}_v1.6$ activity, such as epilepsy and/or epileptic seizure disorder.

Accordingly, in one aspectexample, this inventiondisclosure is directed to heteroaryl-substituted sulfonamide compounds of formula (I):



wherein:



each n is 1 or 2;

R^1 is an optionally substituted aryl, an optionally substituted monocyclic heteroaryl or an optionally substituted bicyclic heteroaryl;

R^2 is an optionally substituted 5-membered *N*-heteroaryl or an optionally substituted 6-membered *N*-heteroaryl;

R^3 and R^4 are each independently hydrogen or alkyl;

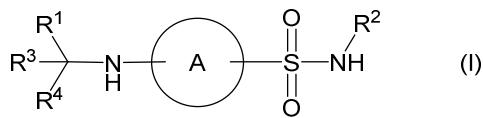
each R^5 and R^6 is independently hydrogen, alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or $-\text{OR}^7$;

R⁷ is hydrogen, alkyl or haloalkyl;

as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;

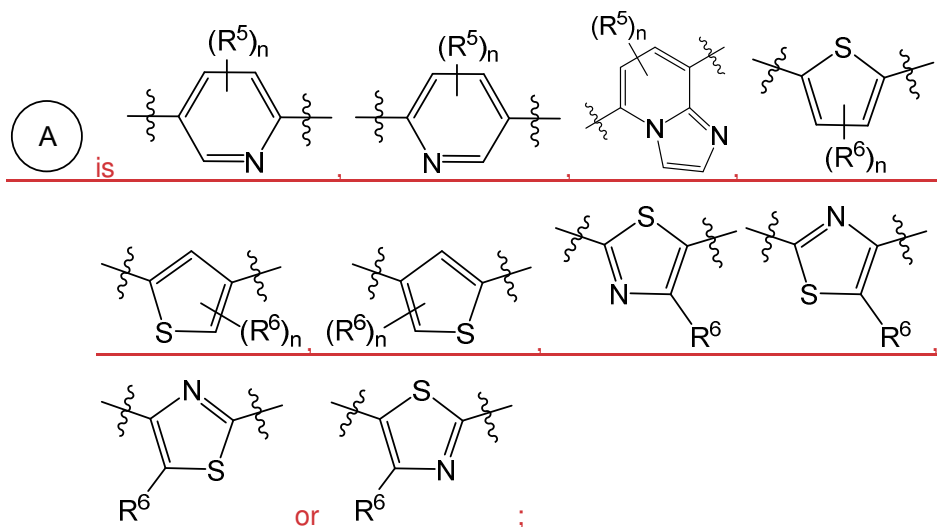
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In one aspect, the disclosure provides a compound of formula (I):



as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or

a pharmaceutically acceptable salt or solvate thereof, wherein:



each n is 1 or 2;

R¹ is an optionally substituted aryl, an optionally substituted monocyclic heteroaryl or an optionally substituted bicyclic heteroaryl;

15 R² is an optionally substituted 5-membered N-heteroaryl or an optionally substituted 6-membered N-heteroaryl;

R³ and R⁴ are each independently hydrogen or alkyl;

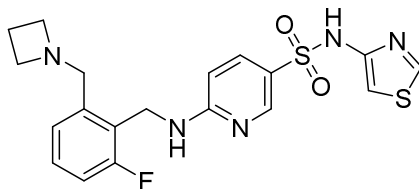
each R⁵ is independently alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or -OR⁷;

20 each R⁶ is independently hydrogen, alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or -OR⁷; and

R⁷ is hydrogen, alkyl or haloalkyl.

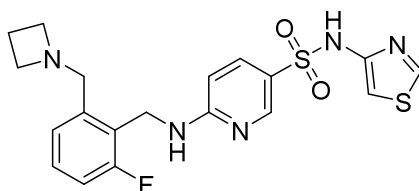
In one aspect, the disclosure provides a compound, which is 5-((3,6-difluoro-2-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(thiazol-4-yl)imidazo[1,2-a]pyridine-8-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

5 In one aspect, the disclosure provides a compound, which is 6-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide, represented by the formula:



10 as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the disclosure provides a compound, which is 6-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide, represented by the formula:



15 or a pharmaceutically acceptable salt thereof.

The compounds of the inventiondisclosure, which are compounds of formula (I) as described above, as individual stereoisomers, enantiomers or tautomers thereof or mixtures thereof; or as pharmaceutically acceptable salts, solvates or prodrugs thereof, are useful in treating diseases or conditions associated with voltage-gated sodium channels, preferably Na_v1.6. Preferably, the compounds of the inventiondisclosure are Na_v1.6 inhibitors. More preferably, the compounds of the inventiondisclosure show selectivity of inhibiting Na_v1.6 as compared with inhibiting Na_v1.5 and/or Na_v1.1. Without wishing to be bound by theory, such selectivity is thought to advantageously reduce any side effects which may be associated with the inhibition of Na_v1.5 and/or Na_v1.1.

In another aspectexample, the inventiondisclosure provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of formula (I), as described above, as a stereoisomer, enantiomer or tautomer thereof or

mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In one aspect, the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound as disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

In another ~~aspect~~example, the ~~invention~~disclosure provides methods for the treatment of a sodium channel-mediated disease or condition in a mammal, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the ~~invention~~disclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the ~~invention~~disclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another ~~aspect~~example, the ~~invention~~disclosure provides methods for the treatment of epilepsy and/or epileptic seizure disorder in a mammal, preferably a human, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the ~~invention~~disclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the ~~invention~~disclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspectexample, the present inventiondisclosure provides a method for treating or lessening the severity of a disease, condition, or disorder in a mammal where activation or hyperactivity of Na_v1.6 is implicated in the disease, condition or disorder, wherein the method comprises administering to the mammal in need thereof
5 a therapeutically effective amount of a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer
10 thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspectexample, the inventiondisclosure provides methods of treating or ameliorating, but not preventing, epilepsy and/or epileptic seizure disorder in a mammal, wherein the methods comprise administering to the mammal in need thereof
15 a therapeutically effective amount of a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer
20 thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspectexample, the inventiondisclosure provides methods of preparing a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof; or a
25 pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the inventiondisclosure, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspectexample, the inventiondisclosure provides pharmaceutical therapy in combination with one or more other compounds of the inventiondisclosure or one or more other accepted therapies or as any combination thereof to increase the potency of an existing or future drug therapy or to decrease the adverse events associated with the accepted therapy. In one embodimentexample, the present
35 inventiondisclosure relates to a pharmaceutical composition combining compounds of the present inventiondisclosure with established or future therapies for the indications listed herein.

In another ~~aspect~~~~example~~, this ~~invention~~~~disclosure~~ is directed to methods of selectively inhibiting a first voltage-gated sodium channel in a mammal over a second voltage-gated sodium channel, wherein the method comprises administering to the mammal an inhibitory amount of a compound of the ~~invention~~~~disclosure~~, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising an inhibitory amount of a compound of the ~~invention~~~~disclosure~~, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In one aspect, the disclosure provides an *in vitro* method of decreasing ion flux through Na_v1.6 in a mammalian cell, wherein the method comprises contacting the cell with a compound as disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the disclosure provides use of a compound as disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for decreasing ion flux through Na_v1.6 in a mammalian cell.

In one aspect, the disclosure provides use of a compound as disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for selectively inhibiting a first voltage-gated sodium channel over a second voltage-gated sodium channel in a mammal.

In one aspect, the disclosure provides use of a compound as disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or a condition associated with Na_v1.6 activity in a mammal, wherein the disease or condition is epilepsy or epileptic seizure disorder.

In another ~~aspect~~~~example~~, this ~~invention~~~~disclosure~~ is directed to the use of the compounds of the ~~invention~~~~disclosure~~, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or the use of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of the ~~invention~~~~disclosure~~, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment of a disease or condition associated with the activity of a voltage-gated sodium channel, preferably Na_v1.6, in a mammal and preferably wherein the disease or condition is epilepsy and/or epileptic seizure disorder.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

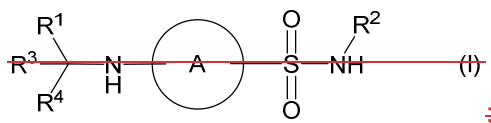
Certain chemical groups named herein may be preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C₇-C₁₂alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C₄-C₁₂cycloalkylalkyl describes a cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described.

In addition to the foregoing, as used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

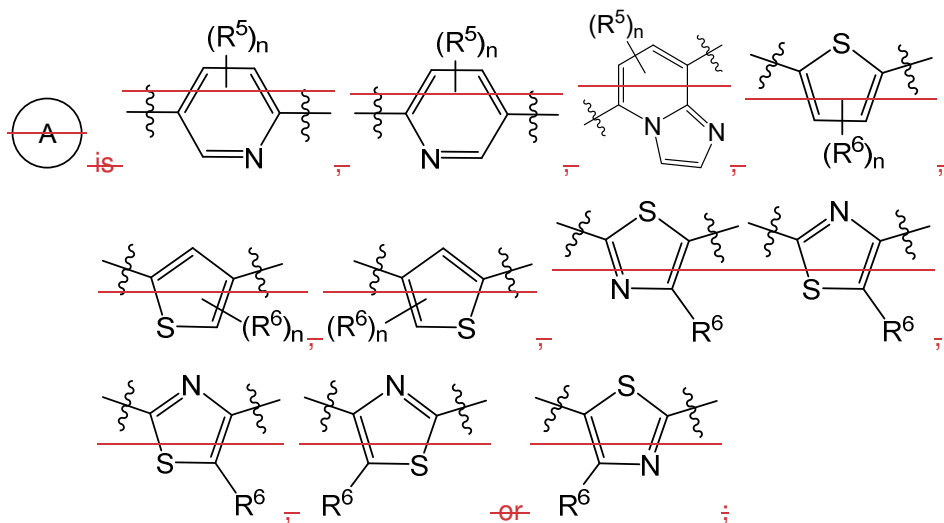
"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight carbon atoms, more preferably one to six

WHAT IS CLAIMED IS

1. ~~A compound of formula (I):~~



wherein:



each n is 1 or 2;

~~R¹ is an optionally substituted aryl, an optionally substituted monocyclic heteroaryl or an optionally substituted bicyclic heteroaryl;~~

~~R² is an optionally substituted 5-membered N-heteroaryl or an optionally substituted 6-membered N-heteroaryl;~~

~~R³ and R⁴ are each independently hydrogen or alkyl;~~

~~each R⁵ and R⁶ is independently hydrogen, alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or —OR⁷; and~~

~~R⁷ is hydrogen, alkyl or haloalkyl;~~

~~as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;~~

~~or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

2. ~~The compound of Claim 1, wherein:~~



~~n is as defined above in Claim 1;~~

~~R¹ is aryl optionally substituted by one or more substituents selected from alkyl, halo, haloalkyl, -R⁸-N(R⁹)R¹⁰ and optionally substituted *N*-heterocyclalkyl;~~

~~R² is as defined above in Claim 1;~~

~~R³ and R⁴ are each hydrogen or alkyl;~~

~~R⁵, R⁶ and R⁷ are each as defined above in Claim 1;~~

~~R⁸ is a direct bond or an optionally substituted straight or branched alkylene chain; and~~

~~R⁹ and R¹⁰ are each independently hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl.~~

~~3. — The compound of Claim 2, wherein:~~



~~is as defined above in Claim 2;~~

~~n is as defined above in Claim 2;~~

~~R¹ is phenyl optionally substituted by one or more substituents selected from halo, -R⁸-N(R⁹)R¹⁰ or optionally substituted *N*-heterocyclalkyl;~~

~~R² is as defined above in Claim 2;~~

~~R³ and R⁴ are each hydrogen or alkyl;~~

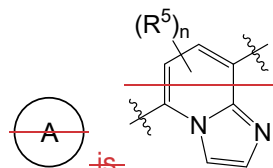
~~R⁵, R⁶ and R⁷ is as defined above in Claim 2;~~

~~R⁸ is an optionally straight or branched alkylene chain;~~

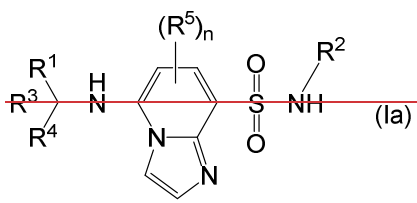
~~R⁹ is hydrogen or alkyl; and~~

~~R¹⁰ is hydrogen or alkyl.~~

~~4. — The compound of Claim 3, wherein:~~



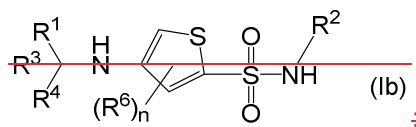
~~is~~, wherein the compound has the following formula (Ia):



wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

5. The compound of Claim 4 which is 5-((3,6-difluoro-2-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(thiazol-4-yl)imidazo[1,2-*a*]pyridine-8-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

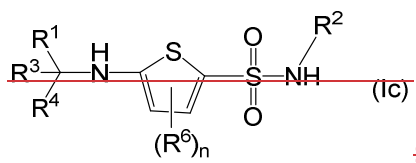
6. The compound of Claim 3, wherein:



wherein n , R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

7. The compound of Claim 6 which is 4-((2-bromo-6-fluorobenzyl)amino)-*N*-(6-fluoropyridin-2-yl)-5-methylthiophene-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

8. The compound of Claim 3, wherein:

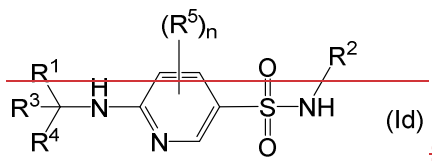


wherein n , R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

9. The compound of Claim 8 which is 5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-4-methylthiophene-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a

~~pharmaceutically acceptable salt, solvate or prodrug thereof.~~

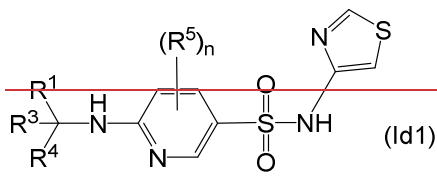
~~10. The compound of Claim 3, wherein:~~



~~wherein n, R¹, R², R³, R⁴, R⁵, R⁷, R⁸, R⁹ and R¹⁰ are each as defined above in Claim 3.~~

~~11. The compound of Claim 10, wherein R² is an optionally substituted 5-membered N-heteroaryl.~~

~~12. The compound of Claim 11, wherein:~~



~~wherein n, R¹, R³, R⁴, R⁵, R⁷, R⁸, R⁹ and R¹⁰ are each as defined above in Claim 3.~~

~~13. The compound of Claim 12 selected from:~~

~~(S)-5-chloro-6-((1-(5-chloro-2-fluorophenyl)ethyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide;~~

~~(S)-5-chloro-6-((1-(2-fluorophenyl)ethyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide;~~

~~6-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide;~~

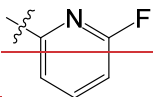
~~6-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-2-methyl-N-(thiazol-4-yl)pyridine-3-sulfonamide;~~

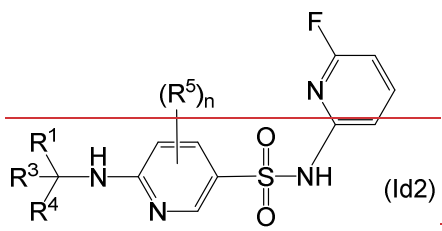
~~6-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-5-methyl-N-(thiazol-4-~~

yl)pyridine-3-sulfonamide;
~~6-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-5-chloro-*N*-(thiazol-4-yl)pyridine-3-sulfonamide; and~~
~~6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-2-methyl-*N*-(thiazol-4-yl)pyridine-3-sulfonamide;~~
 as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

14. The compound of Claim 10, wherein R^2 is an optionally substituted 6-membered *N*-heteroaryl.

15. The compound of Claim 11, wherein:

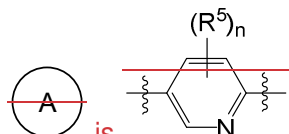
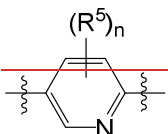
R^2 is , wherein the compound has the following structure (Id2):

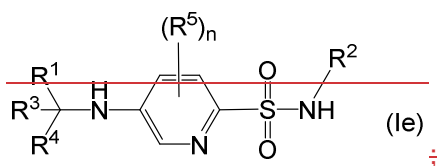


wherein n , R^1 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

16. The compound of Claim 15 selected from:
~~6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-2-methylpyridine-3-sulfonamide; and~~
~~5-chloro-6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)pyridine-3-sulfonamide;~~
 as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

17. The compound of Claim 3, wherein:

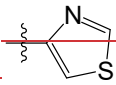
 is , wherein the compound has the following formula (Ic):

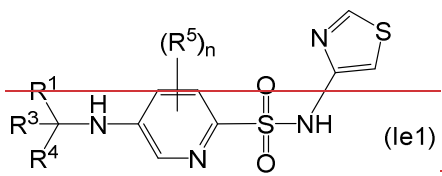


wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

18. The compound of Claim 17, wherein R^2 is an optionally substituted 5-membered *N*-heteroaryl.

19. The compound of Claim 18, wherein:

R^2 is , wherein the compound has the following structure (Ie1):



wherein n , R^1 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 3.

20. The compound of Claim 19 selected from:

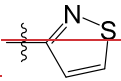
(*S*)-5-((1-(2-fluorophenyl)ethyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-4-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-((2,2-dimethylazetidin-1-yl)methyl)-6-fluorobenzyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 5-((2-(azetidin-1-ylmethyl)-3-fluorobenzyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;
 4-(difluoromethyl)-5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(thiazol-4-yl)pyridine-2-sulfonamide;

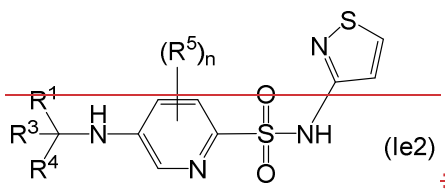
~~6-(difluoromethyl)-5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-fluoro-6-((3-methylazetidin-1-yl)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-((*tert*-butyl(methyl)amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-(azetidin-1-ylmethyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-(((cyclopropylmethyl)(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-fluoro-6-((3-fluoro-3-methylazetidin-1-yl)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-((*tert*-butyl(methyl)amino)methyl)-3,6-difluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-4-(trifluoromethyl)pyridine-2-sulfonamide;~~
~~5-((2-(((1*s*,4*s*)-7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-(((1*s*,4*s*)-7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-bromo-3,6-difluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-3-(trifluoromethyl)benzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;~~
~~5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-6-(trifluoromethyl)pyridine-2-sulfonamide;~~
~~5-((2-((*tert*-butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide; and~~
~~5-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-cyclopropyl-3-fluoro-N-~~

~~(thiazol-4-yl)pyridine-2-sulfonamide;~~

~~as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

~~21. The compound of Claim 18, wherein:~~

~~R² is , wherein the compound has the following structure (Ie2):~~



~~wherein n, R¹, R³, R⁴, R⁵, R⁷, R⁸, R⁹ and R¹⁰ are each as defined above in Claim 3.~~

~~22. The compound of Claim 21 selected from:~~

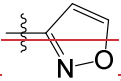
~~5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-4-methylpyridine-2-sulfonamide;~~

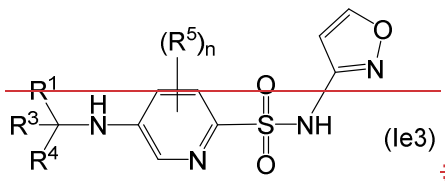
~~5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-6-methylpyridine-2-sulfonamide; and~~

~~5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-6-methylpyridine-2-sulfonamide;~~

~~as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

~~23. The compound of Claim 18, wherein:~~

~~R² is , wherein the compound has the following structure (Ie3):~~



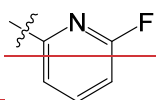
~~wherein n, R¹, R³, R⁴, R⁵, R⁷, R⁸, R⁹ and R¹⁰ are each as defined above in Claim 3.~~

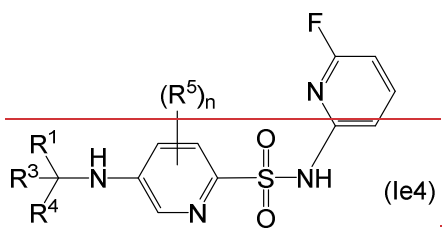
~~24. The compound of Claim 23 which is 5-((2-((tert~~

~~butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-N-(isoxazol-3-yl)-6-methylpyridine-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

25.——The compound of Claim 15, wherein R² is an optionally substituted 6-membered *N*-heteroaryl.

26.——The compound of Claim 25, wherein:

R² is , wherein the compound has the following structure (Ie4):



wherein *n*, R¹, R³, R⁴, R⁵, R⁷, R⁸, R⁹ and R¹⁰ are each as defined above in Claim 3.

27.——The compound of Claim 24 selected from:

~~5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;~~

~~5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;~~

~~5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide;~~

~~5-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-N-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide;~~

~~5-((2-((*tert*-butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-N-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide; and~~

~~3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-N-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;~~

~~as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

28.——The compound of Claim 1, wherein:



~~is as defined above in Claim 1.~~

~~n is as defined above in Claim 1;~~

~~R¹ is a bicyclic heteroaryl optionally substituted by one or more substituents selected from alkyl, halo, haloalkyl, -R⁸-N(R⁹)R¹⁰ and optionally substituted N-heterocyclalkyl;~~

~~R² is as defined above in Claim 1;~~

~~R³ and R⁴ are each hydrogen or alkyl;~~

~~R⁵, R⁶ and R⁷ are each as defined above in Claim 1;~~

~~R⁸ is a direct bond or an optionally substituted straight or branched alkylene chain; and~~

~~R⁹ and R¹⁰ are each independently hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl.~~

29. The compound of Claim 2, wherein:



~~is as defined above in Claim 28;~~

~~n is as defined above in Claim 28;~~

~~R¹ is isoquinoliny optionally substituted by one or more substituents selected from halo, -R⁸-N(R⁹)R¹⁰ or optionally substituted N-heterocyclalkyl;~~

~~R² is as defined above in Claim 28;~~

~~R³ and R⁴ are each hydrogen or alkyl;~~

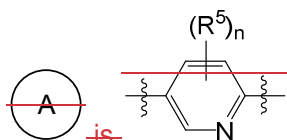
~~R⁵, R⁶ and R⁷ is as defined above in Claim 28;~~

~~R⁸ is an optionally straight or branched alkylene chain;~~

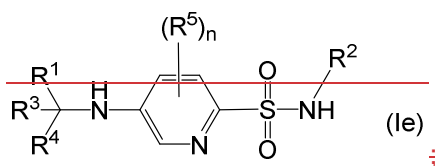
~~R⁹ is hydrogen or alkyl; and~~

~~R¹⁰ is hydrogen or alkyl.~~

30. The compound of Claim 29, wherein:



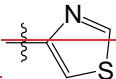
~~is~~ ~~wherein the compound has the following formula (Ie):~~

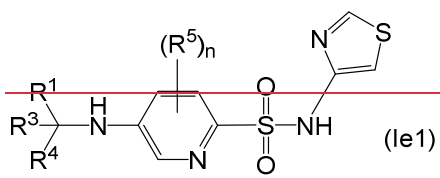


wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 29.

31. The compound of Claim 30, wherein R^2 is an optionally substituted 5-membered *N*-heteroaryl.

32. The compound of Claim 31, wherein:

R^2 is , wherein the compound has the following structure (le1):



wherein n , R^1 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 and R^{10} are each as defined above in Claim 29.

33. The compound of Claim 32 which is 5-((isoquinolin-8-ylmethyl)amino)-6-methyl-*N*-(thiazol-4-yl)pyridine-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

34. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of Claims 1-33, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

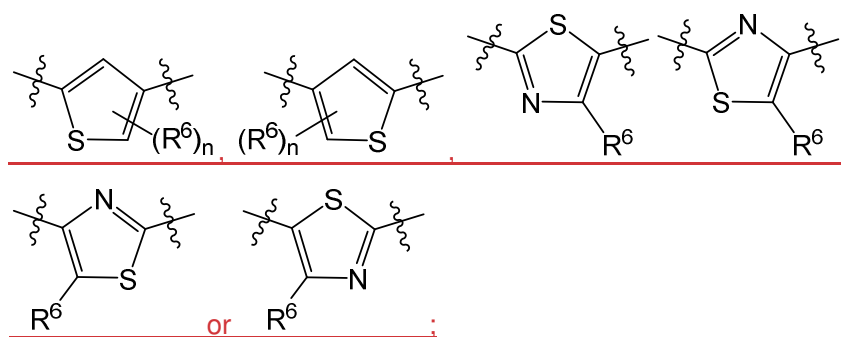
35. A method of treating a disease or a condition associated with Na_v1.6 activity in a mammal wherein the disease or condition is epilepsy and/or epileptic seizure disorder and wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of any one of Claims 1-

~~36. A method of decreasing ion flux through Na_v1.6 in a mammalian cell, wherein the method comprises contacting the cell with a compound of any one of Claims 1-33, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.~~

~~38.—The method of Claim 37 wherein the first voltage-gated sodium channel is Nav1.6.~~

40.—The method of Claim 37 wherein the second voltage-gated sodium channel is Na_v1.1.

$$\begin{array}{c} \text{R}^1 \\ \text{R}^3 \diagdown \quad \diagup \text{R}^4 \\ \text{C} - \text{NH} - \text{A} - \text{SO}_2 - \text{NH} - \text{R}^2 \end{array} \quad (\text{I})$$



each n is 1 or 2;

R¹ is an optionally substituted aryl, an optionally substituted monocyclic heteroaryl or an optionally substituted bicyclic heteroaryl;

R² is an optionally substituted 5-membered N-heteroaryl or an optionally substituted 6-membered N-heteroaryl;

R³ and R⁴ are each independently hydrogen or alkyl;

each R⁵ is independently alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or –OR⁷;

each R⁶ is independently hydrogen, alkyl, halo, haloalkyl, optionally substituted cycloalkyl, cyano or –OR⁷; and

R⁷ is hydrogen, alkyl or haloalkyl.

2. The compound of Claim 1, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is aryl optionally substituted by one or more substituents selected from alkyl, halo, haloalkyl, –R⁸–N(R⁹)R¹⁰ and optionally substituted N-heterocyclalkyl;

R³ and R⁴ are each hydrogen or alkyl;

R⁸ is a direct bond or an optionally substituted straight or branched alkylene chain; and

R⁹ and R¹⁰ are each independently hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycl, or optionally substituted heterocyclalkyl.

3. The compound of Claim 2, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is phenyl optionally substituted by one or more substituents selected from halo,

-R⁸-N(R⁹)R¹⁰ and optionally substituted *N*-heterocyclalkyl;

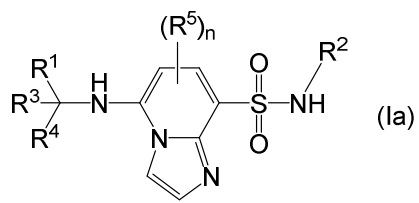
R³ and R⁴ are each hydrogen or alkyl;

R⁸ is an optionally substituted straight or branched alkylene chain;

R⁹ is hydrogen or alkyl; and

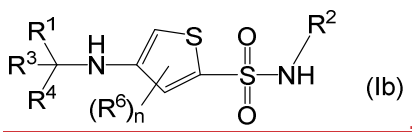
R¹⁰ is hydrogen or alkyl.

4. The compound of Claim 3, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Ia):



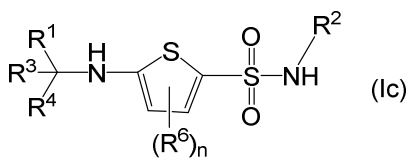
5. A compound, which is 5-((3,6-difluoro-2-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(thiazol-4-yl)imidazo[1,2-*a*]pyridine-8-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of Claim 3, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Ib):



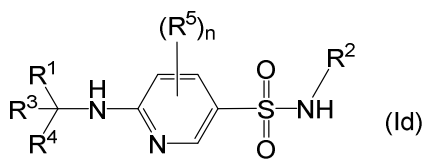
7. The compound of Claim 6, which is 4-((2-bromo-6-fluorobenzyl)amino)-*N*-(6-fluoropyridin-2-yl)-5-methylthiophene-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of Claim 3, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Ic):



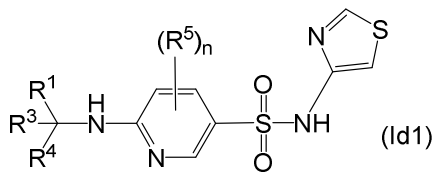
9. The compound of Claim 8, which is 5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(6-fluoropyridin-2-yl)-4-methylthiophene-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of Claim 3, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Id):



11. The compound of Claim 10, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R² is an optionally substituted 5-membered N-heteroaryl.

12. The compound of Claim 11, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Id1):



13. The compound of Claim 12, selected from:

(S)-5-chloro-6-((1-(5-chloro-2-fluorophenyl)ethyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide;

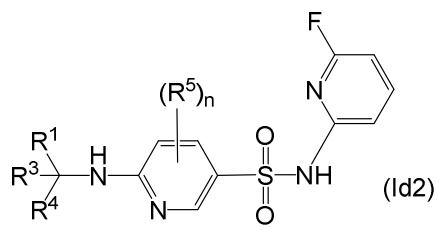
(S)-5-chloro-6-((1-(2-fluorophenyl)ethyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide;

6-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-2-methyl-N-(thiazol-4-

yl)pyridine-3-sulfonamide;
6-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-5-methyl-*N*-(thiazol-4-yl)pyridine-3-sulfonamide;
6-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-5-chloro-*N*-(thiazol-4-yl)pyridine-3-sulfonamide; and
6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-2-methyl-*N*-(thiazol-4-yl)pyridine-3-sulfonamide;
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
or a pharmaceutically acceptable salt or solvate thereof.

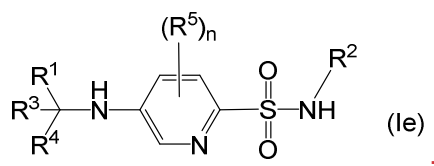
14. The compound of Claim 10, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R² is an optionally substituted 6-membered *N*-heteroaryl.

15. The compound of Claim 14, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Id2):



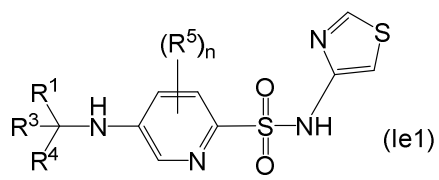
16. The compound of Claim 15, selected from:
6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-2-methylpyridine-3-sulfonamide; and
5-chloro-6-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)pyridine-3-sulfonamide;
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;
or a pharmaceutically acceptable salt or solvate thereof.

17. The compound of Claim 3, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Ie):



18. The compound of Claim 17, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R² is an optionally substituted 5-membered *N*-heteroaryl.

19. The compound of Claim 18, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Ie1):



20. The compound of Claim 19, selected from:

(S)-5-((1-(2-fluorophenyl)ethyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-4-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-((2,2-dimethylazetidin-1-yl)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-(azetidin-1-ylmethyl)-3-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;

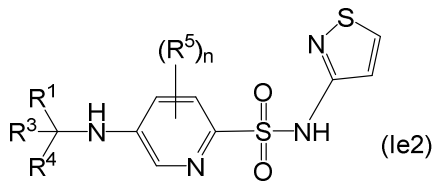
4-(difluoromethyl)-5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(thiazol-4-yl)pyridine-2-sulfonamide;

6-(difluoromethyl)-5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-N-(thiazol-4-yl)pyridine-2-sulfonamide;

5-((2-fluoro-6-((3-methylazetidin-1-yl)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-((tert-butyl(methyl)amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-(azetidin-1-ylmethyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-(((cyclopropylmethyl)(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-fluoro-6-((3-fluoro-3-methylazetidin-1-yl)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-((tert-butyl(methyl)amino)methyl)-3,6-difluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-4-(trifluoromethyl)pyridine-2-sulfonamide;
5-((2-(((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-(((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-bromo-3,6-difluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-3-(trifluoromethyl)benzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide;
5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-6-(trifluoromethyl)pyridine-2-sulfonamide;
5-((2-((tert-butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide; and
5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-6-cyclopropyl-3-fluoro-N-(thiazol-4-yl)pyridine-2-sulfonamide;
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof;

or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of Claim 18, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Ie2):



22. The compound of Claim 21, selected from:

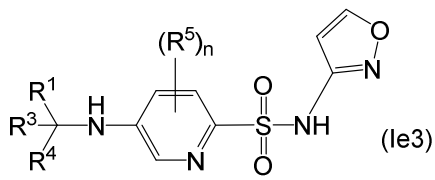
5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-4-methylpyridine-2-sulfonamide;

5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-6-methylpyridine-2-sulfonamide; and

5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-N-(isothiazol-3-yl)-6-methylpyridine-2-sulfonamide;

as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

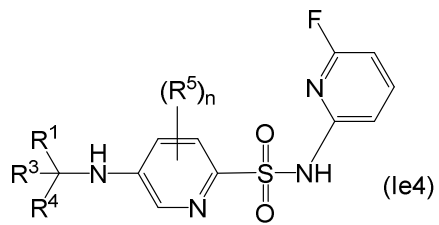
23. The compound of Claim 18, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Ie3):



24. The compound of Claim 23, which is 5-((2-((tert-butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-N-(isoxazol-3-yl)-6-methylpyridine-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of Claim 17, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R² is an optionally substituted 6-membered *N*-heteroaryl.

26. The compound of Claim 25, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Ie4):



27. The compound of Claim 26, selected from:

5-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-*N*-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;

5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;

5-((2-fluoro-6-(pyrrolidin-1-ylmethyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide;

5-((2-((*tert*-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-*N*-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide;

5-((2-((*tert*-butyl(methyl)amino)methyl)benzyl)amino)-3-fluoro-*N*-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide; and

3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)amino)methyl)benzyl)amino)-*N*-(6-fluoropyridin-2-yl)-4-methylpyridine-2-sulfonamide;

as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

28. The compound of Claim 1, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is a bicyclic heteroaryl optionally substituted by one or more substituents selected from alkyl, halo, haloalkyl, -R⁸-N(R⁹)R¹⁰ and optionally substituted *N*-heterocyclylalkyl;

R³ and R⁴ are each hydrogen or alkyl;

R⁸ is a direct bond or an optionally substituted straight or branched alkylene chain; and

R⁹ and R¹⁰ are each independently hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, or optionally substituted heterocyclalkyl.

29. The compound of Claim 2, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ is isoquinolinyl optionally substituted by one or more substituents selected from halo, -R⁸-N(R⁹)R¹⁰ and optionally substituted *N*-heterocyclalkyl;

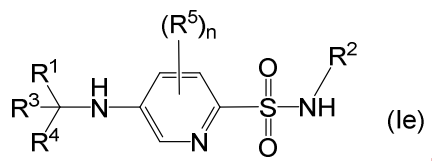
R³ and R⁴ are each hydrogen or alkyl;

R⁸ is an optionally substituted straight or branched alkylene chain;

R⁹ is hydrogen or alkyl; and

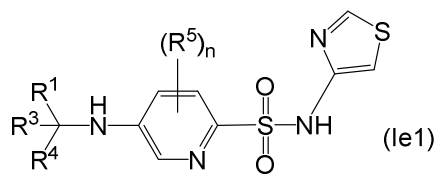
R¹⁰ is hydrogen or alkyl.

30. The compound of Claim 29, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following formula (Ie):



31. The compound of Claim 30, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R² is an optionally substituted 5-membered *N*-heteroaryl.

32. The compound of Claim 31, as an individual stereoisomer, enantiomer, or tautomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure (Ie1):



33. The compound of Claim 32, which is 5-((isoquinolin-8-ylmethyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide; as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

34. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Claim 1, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

35. Use of a compound of Claim 1, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or a condition associated with Na_v1.6 activity in a mammal, wherein the disease or condition is epilepsy or epileptic seizure disorder.

36. An *in vitro* method of decreasing ion flux through Na_v1.6 in a mammalian cell, wherein the method comprises contacting the cell with a compound of Claim 1, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

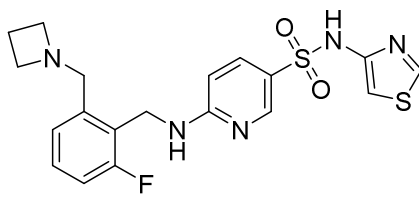
37. Use of a compound of Claim 1, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for selectively inhibiting a first voltage-gated sodium channel over a second voltage-gated sodium channel in a mammal.

38. The use of Claim 37 wherein the first voltage-gated sodium channel is Na_v1.6.

39. The use of Claim 37 wherein the second voltage-gated sodium channel is Na_v1.5.

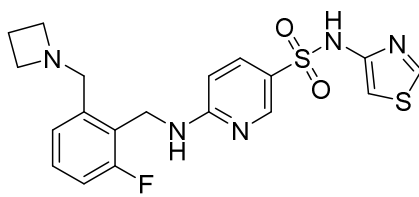
40. The use of Claim 37 wherein the second voltage-gated sodium channel is Na_v1.1.

41. A compound, which is 6-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide, represented by the formula:



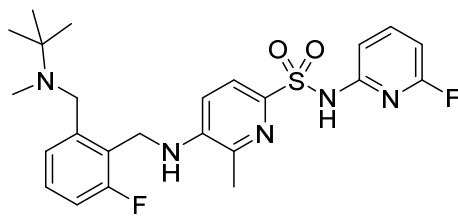
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

42. A compound, which is 6-((2-(azetidin-1-ylmethyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)pyridine-3-sulfonamide, represented by the formula:



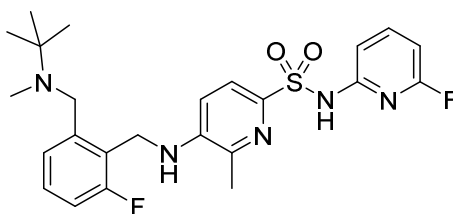
or a pharmaceutically acceptable salt thereof.

43. The compound of Claim 1, which is 5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-N-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide, represented by the formula:



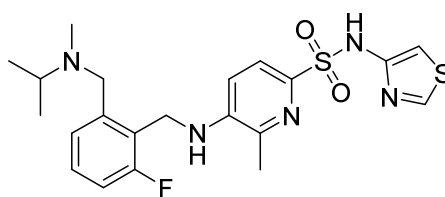
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

44. The compound of Claim 1, which is 5-((2-((tert-butyl(methyl)amino)methyl)-6-fluorobenzyl)amino)-N-(6-fluoropyridin-2-yl)-6-methylpyridine-2-sulfonamide, represented by the formula:



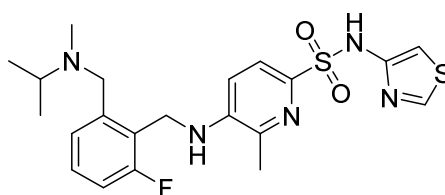
or a pharmaceutically acceptable salt thereof.

45. The compound of Claim 1, which is 5-((2-fluoro-6-((isopropyl(methyl)-amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



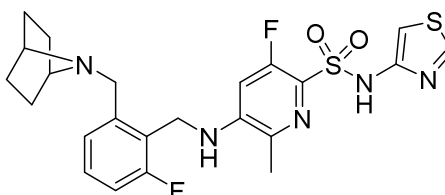
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

46. The compound of Claim 1, which is 5-((2-fluoro-6-((isopropyl(methyl)-amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



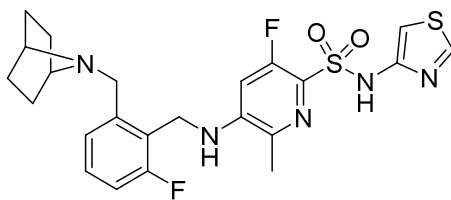
or a pharmaceutically acceptable salt thereof.

47. The compound of Claim 1, which is 5-((2-((azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



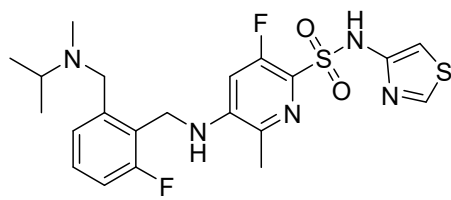
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

48. The compound of Claim 1, which is 5-((2-((azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



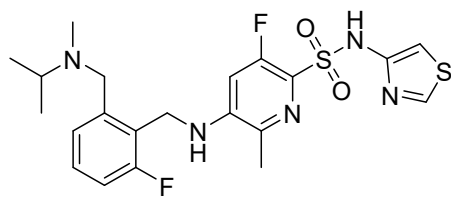
or a pharmaceutically acceptable salt thereof.

49. The compound of Claim 1, which is 3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)-amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



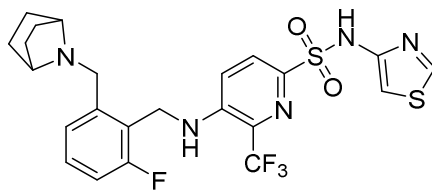
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

50. The compound of Claim 1, which is 3-fluoro-5-((2-fluoro-6-((isopropyl(methyl)-amino)methyl)benzyl)amino)-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



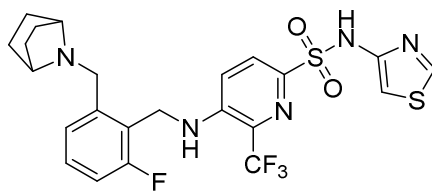
or a pharmaceutically acceptable salt thereof.

51. The compound of Claim 1, which is 5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-6-(trifluoromethyl)pyridine-2-sulfonamide, represented by the formula:



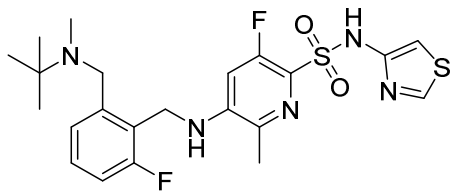
as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

52. The compound of Claim 1, which is 5-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-N-(thiazol-4-yl)-6-(trifluoromethyl)pyridine-2-sulfonamide, represented by the formula:



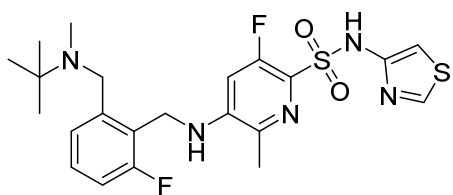
or a pharmaceutically acceptable salt thereof.

53. The compound of Claim 1, which is 5-((2-((tert-butyl(methyl)amino)-methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

54. The compound of Claim 1, which is 5-((2-((tert-butyl(methyl)amino)-methyl)-6-fluorobenzyl)amino)-3-fluoro-6-methyl-N-(thiazol-4-yl)pyridine-2-sulfonamide, represented by the formula:



or a pharmaceutically acceptable salt thereof.

55. Use of a compound of Claim 1, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for decreasing ion flux through Na_v1.6 in a mammalian cell.