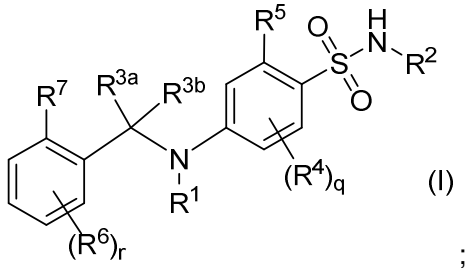
available Na_V blocking drugs.

There is therefore an unmet medical need to treat epilepsy and other $Na_V1.6$ associated pathological states effectively and without adverse side effects due to the blocking of other sodium channels, such as $Na_V1.1$ and/or $Na_V1.5$. The present invention provides methods to meet these critical needs.

SUMMARY

The present disclosure is directed to benzenesulfonamide compounds and pharmaceutical compositions comprising the compounds and methods of using the compounds and the pharmaceutical compositions of the disclosure for the treatment of diseases or conditions associated with the activity of voltage-gated sodium channels, particularly, $Na_V1.6$ activity, such as epilepsy and/or epileptic seizure disorder.

Accordingly, in one example, this disclosure is directed to compounds of formula (I):



(I)

;

wherein:

q is 1 or 2;

r is 1 or 2;

R^1 is hydrogen or alkyl;

R^2 is thiazolyl, isothiazolyl or isoxazolyl;

R^{3a} and R^{3b} are each independently hydrogen or alkyl;

each R^4 is independently halo or alkyl;

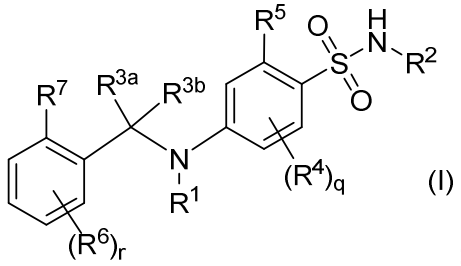
R^5 is halo;

each R^6 is independently halo or alkoxy;

R^7 is azabicyclo[2.2.1]heptanylalkyl or R^7 is ((methyl)(prop-2-yl)amino)alkyl when r is 2 and at least one R^6 is alkoxy;

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 present disclosure refers to a compound of formula (I):



(I)

;

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

q is 1 or 2;

r is 1 or 2;

R^1 is hydrogen or alkyl;

R^2 is thiazolyl, isothiazolyl or isoxazolyl;

R^{3a} and R^{3b} are each independently hydrogen or alkyl;

each R^4 is independently halo or alkyl;

R^5 is halo;

each R^6 is independently halo or alkoxy; and

R^7 is azabicyclo[2.2.1]heptanylalkyl or R^7 is ((methyl)(prop-2-yl)amino)alkyl when r is 2 and at least one R^6 is alkoxy.

The compounds of the disclosure, 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 disclosure are $Na_V1.6$ inhibitors. More preferably, the compounds of the disclosure 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 example, the disclosure 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 present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound disclosed herein, as a stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

In another example, the 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 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 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 example, the present disclosure 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 a therapeutically effective amount of a compound of the 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 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 example, the disclosure 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 a therapeutically effective amount of a compound of the 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 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.

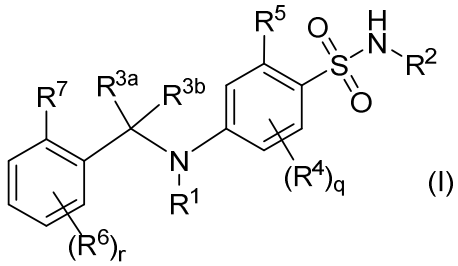
In another example, the disclosure provides pharmaceutical therapy in combination with one or more other compounds of the disclosure or one or more other accepted therapies or as any combination thereof to increase the potency of an existing or future drug therapy or to decrease the adverse events associated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

In another example, this 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 a inhibitory amount of a compound of the 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 inhibitory amount of a compound of the 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 example, this disclosure is directed to the use of the compounds of the 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 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.

WHAT IS CLAIMED IS

1. A compound of formula (I):



(I)

;

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

q is 1 or 2;

r is 1 or 2;

R^1 is hydrogen or alkyl;

R^2 is thiazolyl, isothiazolyl or isoxazolyl;

R^{3a} and R^{3b} are each independently hydrogen or alkyl;

each R^4 is independently halo or alkyl;

R^5 is halo;

each R^6 is independently halo or alkoxy; and

R^7 is azabicyclo[2.2.1]heptanylalkyl or R^7 is ((methyl)(prop-2-yl)amino)alkyl when r is 2 and at least one R^6 is alkoxy.

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 R^7 is azabicyclo[2.2.1]heptanylalkyl.

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 R^2 is isothiazolyl.

4. The compound of Claim 3 selected from:

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isothiazol-3-yl)benzenesulfonamide; and

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-*N*-

(isothiazol-3-yl)benzenesulfonamide;

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

5. 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 R^2 is thiazolyl.

6. The compound of Claim 5, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein r is 1.

7. The compound of Claim 6 selected from:

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-3-chloro-2-fluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-3-methyl-*N*-(thiazol-4-yl)benzenesulfonamide; and

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

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 5, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, where r is 2.

9. The compound of Claim 8 selected from:

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-3,6-difluorobenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,3-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

54-((2-(1-(7-azabicyclo[2.2.1]heptan-7-yl)ethyl)-3,6-difluorobenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

(*S*)-4-((2-(1-(7-azabicyclo[2.2.1]heptan-7-yl)ethyl)-3,6-difluorobenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide; and

(*R*)-4-((2-(1-(7-azabicyclo[2.2.1]heptan-7-yl)ethyl)-3,6-difluorobenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide;

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 2, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is isoxazolyl.

11. The compound of Claim 10 selected from:

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide; and

4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide;

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

12. 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, where R^7 is ((methyl)(prop-2-yl)amino)alkyl, provided that r is 2 and at least one R^6 is alkoxy.

13. The compound of Claim 12, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is isothiazolyl.

14. The compound of Claim 12, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is thiazolyl.

15. The compound of Claim 14 selected from:

2,6-difluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide;

2,6-difluoro-4-((6-fluoro-3-isopropoxy-2-((isopropyl(methyl)amino)methyl)benzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide;

2,3-difluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide;

5-chloro-2-fluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide; and

2-fluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-5-methyl-*N*-(thiazol-4-yl)benzenesulfonamide;

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

16. The compound of Claim 12, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is isoxazolyl.

17. 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.

18. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isothiazol-3-yl)benzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

19. The compound of Claim 1, which is 2,6-difluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide, 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 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide, 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 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-3-methyl-*N*-(thiazol-4-yl)benzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

24. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide, 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 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,3-difluoro-N-(thiazol-4-yl)benzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-N-(isothiazol-3-yl)benzenesulfonamide, as an individual stereoisomer, enantiomer or tautomer thereof or a mixture thereof; or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of Claim 1, which is 2-fluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-5-methyl-N-(thiazol-4-

yl)benzenesulfonamide, 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, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isothiazol-3-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

29. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isothiazol-3-yl)benzenesulfonamide.

30. The compound of Claim 1, which is 2,6-difluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

31. The compound of Claim 1, which is 2,6-difluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-*N*-(thiazol-4-yl)benzenesulfonamide.

32. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

33. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide.

34. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

35. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,6-difluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide.

36. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-*N*-(isoxazol-3-yl)-3-

methylbenzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

37. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-*N*-(isoxazol-3-yl)-3-methylbenzenesulfonamide.

38. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-3-methyl-*N*-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

39. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2-fluoro-3-methyl-*N*-(thiazol-4-yl)benzenesulfonamide.

40. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

41. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,6-difluoro-*N*-(thiazol-4-yl)benzenesulfonamide.

42. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,3-difluoro-N-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

43. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluoro-3-methoxybenzyl)amino)-2,3-difluoro-N-(thiazol-4-yl)benzenesulfonamide.

44. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-N-(isothiazol-3-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

45. The compound of Claim 1, which is 4-((2-((7-azabicyclo[2.2.1]heptan-7-

yl)methyl)-6-fluorobenzyl)amino)-2,3-difluoro-N-(isothiazol-3-yl)benzenesulfonamide.

46. The compound of Claim 1, which is 2-fluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-5-methyl-N-(thiazol-4-yl)benzenesulfonamide, or a pharmaceutically acceptable salt or solvate thereof.

47. The compound of Claim 1, which is 2-fluoro-4-((6-fluoro-2-((isopropyl(methyl)amino)methyl)-3-methoxybenzyl)amino)-5-methyl-N-(thiazol-4-yl)benzenesulfonamide.