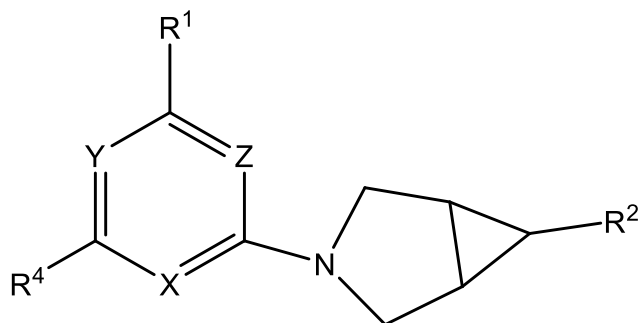


CLAIMS

It is claimed:

1. A compound of Formula I



or a pharmaceutically salt thereof, wherein

Y is N or C-CN;

Z is N or CH;

X is N or CR³;

provided that at least one of Y, Z, or X is N;

R¹ is C₃₋₇-cycloalkyl or a 4- to 7-membered heterocyclic moiety, wherein the heterocyclic moiety contains 1 to 2 atoms independently selected from nitrogen, oxygen and sulfur, and wherein the cycloalkyl or heterocyclic moiety has 0 to 3 substituents independently selected from -C₁₋₃alkyl, and -OH, provided that there is no more than one -OH substituent; or

N(C₁₋₃alkyl)₂, NH(C₁₋₃alkyl), or NH(C₃₋₄cycloalkyl), wherein each C₁₋₃alkyl is substituted with 0 to 1 OH;

R² is -(L)_m-CON(R^N)₂, -(L)_m-SO₂R^S, -L-(CH₂)_nSO₂R^S, -L-(CH₂)_nCO₂H, -L-(CH₂)_nC(O)R^C, -L-(CH₂)_nCONHSO₂R^S, -L-(CH₂)_nSO₂NHCOR^S, -L-(CH₂)_nSO₂NHCONH₂, or -L-(CH₂)_ntetrazol-5-yl;

m is 0 or 1;

n is 0 or 1;

R^N is H or -C₁₋₃alkyl;

R^S is H or -C₁₋₃alkyl;

L is CH₂, CHF, or CF₂;

R^C is -C₁₋₄alkyloxy, -C₁₋₄alkyloxycarbonyloxy-C₁₋₄alkyloxy, or -C₁₋₄alkylcarbonyloxy-C₁₋₄alkyloxy;

R³ is H, halogen, -CN, -C₁₋₃alkyl, -OC₁₋₃alkyl, -C₁₋₃alkyl substituted with 1 to 3 halogen atoms, or -C₃₋₄cycloalkyl; and

R⁴ is cyclopropyl, cyclobutyl, or -C₁₋₃alkyl substituted with 0 to 5 halogen atoms as valency allows.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

Y is N or C-CN;

Z is N or CH;

X is CR³;

provided that at least one of Y or Z is N;

- 5 R¹ is C₃₋₇cycloalkyl or a 4- to 7-membered heterocyclic moiety, wherein the heterocyclic moiety contains 1 to 2 atoms independently selected from nitrogen, oxygen and sulfur, and wherein the cycloalkyl or heterocyclic moiety has 0 to 3 substituents independently selected from -C₁₋₃alkyl, and -OH, provided that there is no more than one -OH substituent; or

10 N(C₁₋₃alkyl)₂, NH(C₁₋₃alkyl), or NH(C₃₋₄cycloalkyl), wherein each C₁₋₃alkyl is substituted with 0 to 1 OH;

 R² is -(L)_m-CON(R^N)₂, -(L)_m-SO₂R^S, -L-(CH₂)_nSO₂R^S, -L-(CH₂)_nCO₂H, -L-(CH₂)_nC(O)R^C, -L-(CH₂)_nCONHSO₂R^S, -L-(CH₂)_nSO₂NHCOR^S, -L-(CH₂)_nSO₂NHCONH₂, or -L-(CH₂)_ntetrazol-5-yl;

 m is 0 or 1;

15 n is 0 or 1;

 R^N is H or -C₁₋₃alkyl;

 R^S is H or -C₁₋₃alkyl;

 L is CH₂, CHF, or CF₂;

20 R^C is -C₁₋₄alkyloxy, -C₁₋₄alkyloxycarbonyloxy-C₁₋₄alkyloxy, or -C₁₋₄alkylcarbonyloxy-C₁₋₄alkyloxy;

 R³ is H, halogen, -CN, -C₁₋₃alkyl, -OC₁₋₃alkyl, -C₁₋₃alkyl substituted with 1 to 3 halogen atoms, or -C₃₋₄cycloalkyl; and

 R⁴ is -C₁₋₃alkyl substituted with 0 to 5 halogen atoms as valency allows.

3. The compound of claim 1 or claim 2, or a pharmaceutically salt thereof, wherein

25 Y is C-CN;

 Z is N;

 X is CR³;

30 R¹ is C₃₋₇cycloalkyl or a 4- to 7-membered heterocyclic moiety, wherein the heterocyclic moiety contains 1 to 2 atoms independently selected from nitrogen, oxygen and sulfur, and wherein the cycloalkyl or heterocyclic moiety has 0 to 3 substituents independently selected from -C₁₋₃alkyl, and -OH, provided that there is no more than one -OH substituent;

 R² is -(L)_m-CON(R^N)₂, -(L)_m-SO₂R^S, -L-(CH₂)_nSO₂R^S, -L-(CH₂)_nCO₂H, -L-(CH₂)_nC(O)R^C, -L-(CH₂)_nCONHSO₂R^S, -L-(CH₂)_nSO₂NHCOR^S, or -L-(CH₂)_ntetrazol-5-yl;

 m is 0 or 1;

35 n is 0 or 1;

 R^N is H or -C₁₋₃alkyl;

R^S is H or $-C_{1-3}$ alkyl;

L is CH_2 , CHF, or CF_2 ;

R^C is $-C_{1-4}$ alkyloxy, $-C_{1-4}$ alkyloxycarbonyloxy- C_{1-4} alkyloxy, or $-C_{1-4}$ alkylcarbonyloxy- C_{1-4} alkyloxy;

5 R^3 is H, halogen, -CN, $-C_{1-3}$ alkyl, $-OC_{1-3}$ alkyl, $-C_{1-3}$ alkyl substituted with 1 to 3 halogen atoms, or $-C_{3-4}$ cycloalkyl; and

R^4 is $-C_{1-3}$ alkyl substituted with 0 to 5 halogen atoms as valency allows.

4. The compound of claims 1, or a pharmaceutically acceptable salt thereof, wherein
Y is N;

10 Z is N;

X is CR^3 ;

R^1 is C_{3-7} cycloalkyl or a 4- to 7-membered heterocyclic moiety, wherein the heterocyclic moiety contains 1 to 2 atoms independently selected from nitrogen, oxygen and sulfur, and wherein the cycloalkyl or heterocyclic moiety has 0 to 3 substituents independently selected
15 from $-C_{1-3}$ alkyl, and $-OH$, provided that there is no more than one $-OH$ substituent;

R^2 is $-(L)_m-CON(R^N)_2$, $-(L)_m-SO_2R^S$, $-L-(CH_2)_nSO_2R^S$, $-L-(CH_2)_nCO_2H$, $-L-(CH_2)_nC(O)R^C$,
 $-L-(CH_2)_nCONHSO_2R^S$, $-L-(CH_2)_nSO_2NHCOR^S$, or $-L-(CH_2)_n$ tetrazol-5-yl;

m is 0 or 1;

n is 0 or 1;

20 R^N is H or $-C_{1-3}$ alkyl;

R^S is H or $-C_{1-3}$ alkyl;

L is CH_2 , CHF, or CF_2 ;

R^C is $-C_{1-4}$ alkyloxy, $-C_{1-4}$ alkyloxycarbonyloxy- C_{1-4} alkyloxy, or $-C_{1-4}$ alkylcarbonyloxy- C_{1-4} alkyloxy;

25 R^3 is H, halogen, -CN, $-C_{1-3}$ alkyl, $-OC_{1-3}$ alkyl, $-C_{1-3}$ alkyl substituted with 1 to 3 halogen atoms, or $-C_{3-4}$ cycloalkyl; and

R^4 is $-C_{1-3}$ alkyl substituted with 0 to 5 halogen atoms as valency allows.

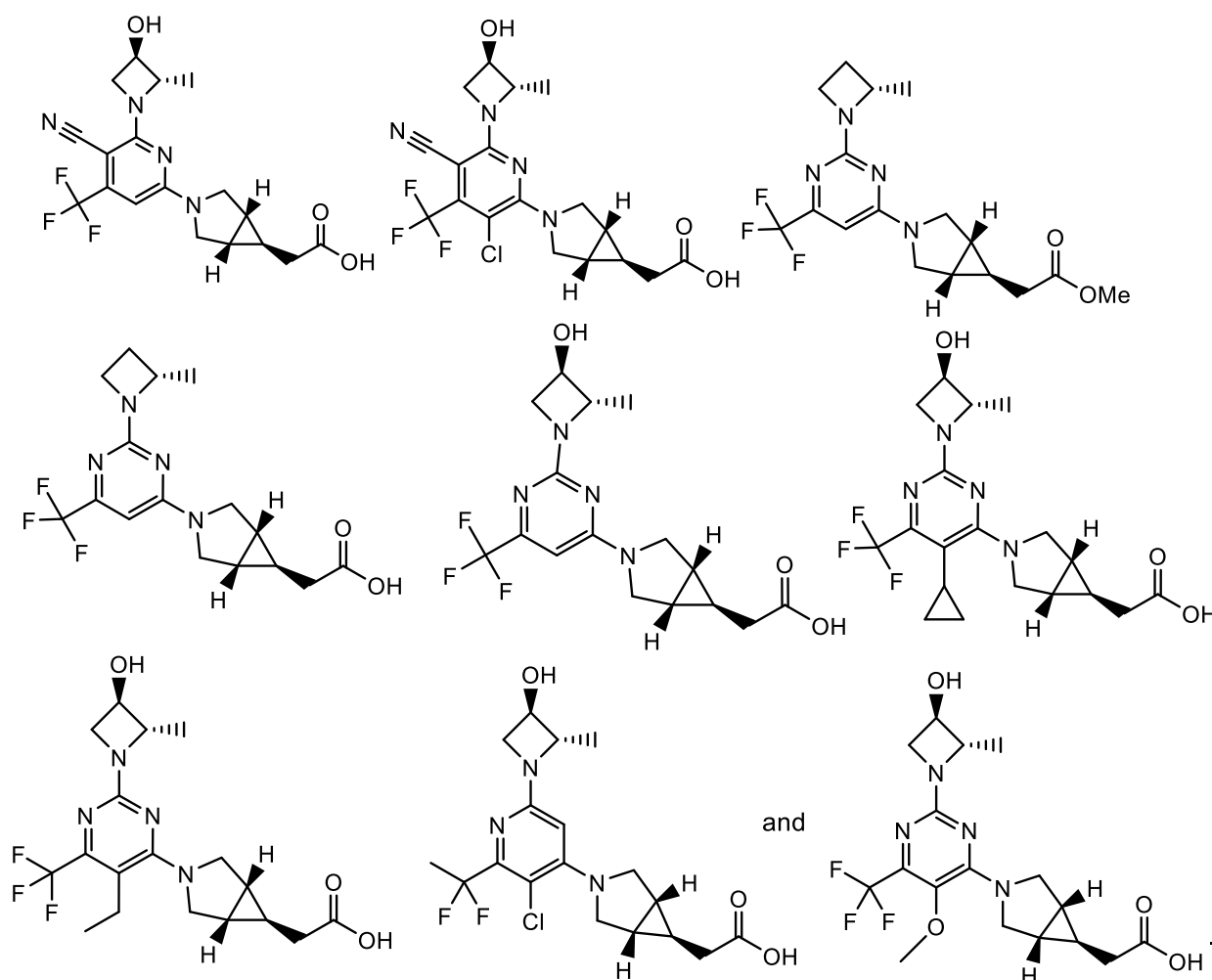
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^S is H or $-CH_3$.

30 6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-CH_2CO_2H$, $-CH_2CO_2CH_3$, or $-CH_2CO_2CH_2CH_3$.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, -Cl, $-CH_3$, $-CH_2CH_3$, $-O-CH_3$, cyclopropyl, or CN.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is -
35 CF_3 , $-CHF_2$, or $-CF_2CH_3$.

9. The compound of claim 1, or a pharmaceutically salt thereof, wherein R¹ is the 4- to 7-membered heterocyclic moiety selected from azetidin-1-yl, pyrrolidin-1-yl, and piperidin-1-yl having 0 to 3 substituents independently selected from -CH₃ and -OH, provided that there is no more than one -OH substituent.
- 5 10. The compound of claim 1, or a pharmaceutically salt thereof, wherein R¹ is azetidin-1-yl, having 1 to 2 -CH₃ substituents and having 0 to 1 -OH substituent, and wherein Y is C-CN and Z is N, or Y and Z are each N.
11. The compound of claim 1, or a pharmaceutically salt thereof, wherein R¹ is cyclobutyl having 0 to 3 substituents independently selected from -CH₃ and -OH, provided that there is
10 no more than one -OH substituent.
12. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein the compound is selected from
[(1R,5S,6R)-3-{5-cyano-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-4-(trifluoromethyl)pyridin-2-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;
15 [(1R,5S,6R)-3-{3-chloro-5-cyano-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-4-(trifluoromethyl)pyridin-2-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;
Methyl [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetate;
[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-
20 azabicyclo[3.1.0]hex-6-yl]acetic acid;
[(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;
[(1R,5S,6R)-3-{5-cyclopropyl-2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;
25 [(1R,5S,6R)-3-{5-ethyl-2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;
[(1R,5S,6R)-3-{3-chloro-2-(1,1-difluoroethyl)-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]pyridin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid; and
[(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-5-methoxy-6-
30 (trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.
13. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein the compound is selected from



14. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein the compound is selected from

(2S,3R)-2,3-dimethyl-1-[4-[(1R,5S,6S)-6-[(methylsulfonyl)methyl]-3-azabicyclo[3.1.0]hex-

5 3-yl]-6-(trifluoromethyl)pyrimidin-2-yl]azetidin-3-ol;

2-[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]-N-(methylsulfonyl)acetamide; and

(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-6-(1H-tetrazol-5-ylmethyl)-3-azabicyclo[3.1.0]hexane.

10 15. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein the compound is selected from

[(1R,5S,6R)-3-{5-cyano-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-4-(trifluoromethyl)pyridin-2-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;

15 [(1R,5S,6R)-3-{3-chloro-5-cyano-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-4-(trifluoromethyl)pyridin-2-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;

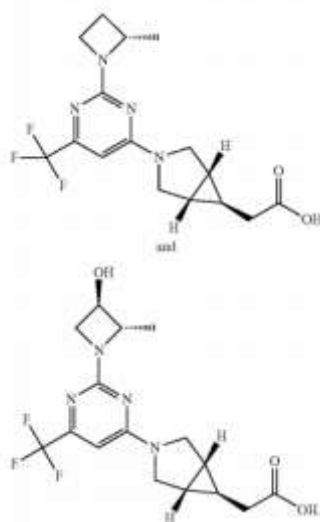
[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;

[(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid;

[(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-5-methyl-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid; and

5 [(1R,5S,6R)-3-{5-cyano-4-(1,1-difluoroethyl)-3-fluoro-6-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]pyridin-2-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

16. The compound of claim 13, or pharmaceutically acceptable salt thereof, wherein the compound is selected from



10 17. A compound, which is [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid, or pharmaceutically acceptable salt thereof.

18. The compound of claim 17, wherein the compound is [(1R,5S,6R)-3-{2-[(2S) 2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

15 19. The compound of claim 17, wherein the compound is a crystalline form of [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

20. The compound of claim 19, wherein the crystalline form is characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2 θ as measured with a copper radiation chosen from 9.0, 10.4, 15.0, and 21.4 +/- 0.2°.

21. A compound, which is [(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid, or pharmaceutically acceptable salt thereof.

22. The compound of claim 21, or pharmaceutically acceptable salt thereof, wherein the compound is [(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

23. The compound of claim 21, wherein the compound is a sodium salt form of [(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

5 24. The compound of claim 21, wherein the compound is a crystalline sodium salt form of [(1R,5S,6R)-3-{2-[(2S,3R)-3-hydroxy-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

25. The compound of claim 24, wherein the crystalline form is characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ as

10 measured with a copper radiation chosen from 5.9, 11.5, 11.8, 13.3, and 21.5 $\pm$ 0.2°.

26. A pharmaceutical composition comprising the compound of Formula I of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.