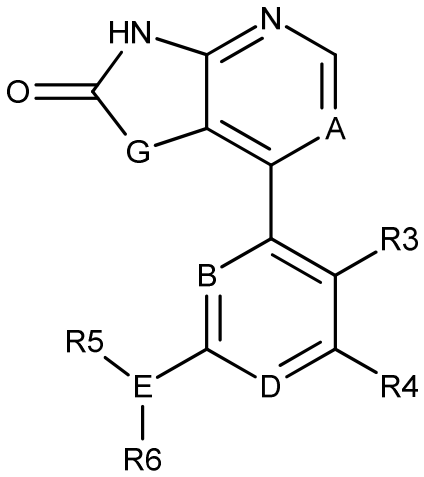
CLAIMS

1. A compound of structural Formula I:



I

or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, wherein:

A is selected from the group consisting of: N, C-R^a, where R^a is selected from hydrogen, halogen, C1-3 alkyl and CN;

B is selected from the group consisting of: N; C-H; C-F and C-(C1-3 alkyl);

D is selected from the group consisting of: N; C-H; C-R^b where R^b is selected from halogen; C1-3 alkyl; and C1-3 haloalkyl;

G is selected from the group consisting of: CR1R2; NR1; and O;

R1 and R2 are independently selected from the group consisting of: hydrogen, halogen, C1-3 alkyl; C3-7 cycloalkyl; C1-3 alkoxyl; C2-6 cycloalkoxyl; C2-6 alkyl alkoxy; hydroxyl; C1-3 alkyl hydroxyl; amino; C1-3 alkyl amino; C1-4 amino alkyl; C2-7 alkyl amino alkyl; C1-3 haloalkyl; aryl; heteroaryl; alkyl aryl and alkyl heteroaryl; or

R1 and R2 together form a 3-5 membered optionally substituted spiro carbocyclic or heterocyclic ring;

R3 is selected from the group consisting of: hydrogen, C1-2 alkyl, OMe and halogen;

R4 is selected from the group consisting of: hydrogen; C1-5 alkyl; C3-7 cycloalkyl; C1-5 haloalkyl; C1-5 alkoxyl; C1-5 haloalkoxyl; alkyl alkoxy; C2-6 heterocycloalkyl; CN and halogen;

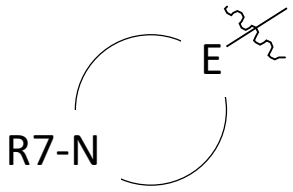
E is selected from the group consisting of: N; C-H; C-R^c, where R^c is selected from the group consisting of halogen; hydroxyl; C1-3 alkyl hydroxyl; C1-3 alkyl amino; C1-3 haloalkyl; C2-6 alkyl alkoxyl; and CN;

R5 and R6 are each independently selected from the group consisting of: hydrogen; C2-5 alkyl; C1-C5 amino alkyl; 4-8-membered amino alkyl ring; C1-9 alkyl alkoxy; C1-9 alkyl amino alkyl; or

R5 and R6 are joined together to form an optionally substituted, optionally bridged Ring Z, wherein Ring Z is a C3-10 heterocycloalkyl mono- or bicyclic ring; or

E, R5 and R6 together are J, wherein J is selected from the group consisting of: N-R^d; C(=O)R^d; SO_2R^d; O-R^d, wherein R^d is a 4-8-membered amino alkyl ring.

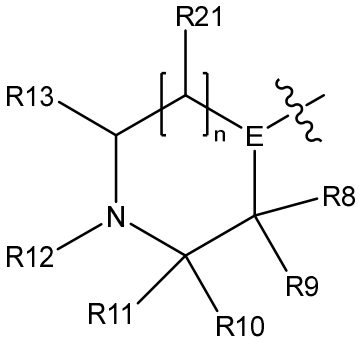
2. The compound of Claim 1, wherein Ring Z is an optionally substituted, optionally bridged, 4-8-membered amino alkyl ring with the general Formula Ia;



Ia

wherein R7 is selected from the group consisting of: hydrogen; C1-3 alkyl; and C1-3 haloalkyl.

3. The compound of Claim 1 or Claim 2, wherein Ring Z is:



wherein R8, R9, R10, R11, R13 and R21 are each independently selected from the group consisting of: hydrogen, C1-3 alkyl, C1-3 alkyl alkoxy; C1-3 alkyl hydroxyl; amino; C1-3 alkyl amino; C1-6 alkyl amino alkyl; C1-3 haloalkyl; alkyl heteroaryl;

R12 is selected from the group consisting of: hydrogen; C1-3 alkyl; and C1-3 haloalkyl; or

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R12, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

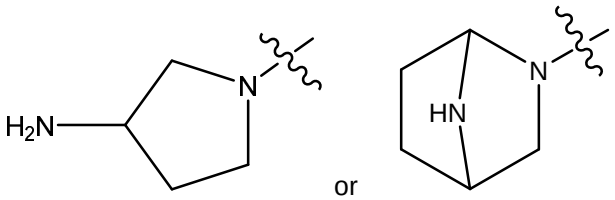
n is selected from the group consisting of: 0; 1; and 2.

4. The compound of any one of Claims 1 to 3, wherein:

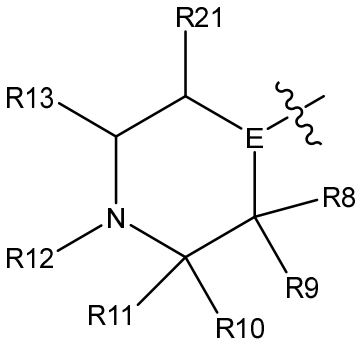
n=0; and

E is selected from the group consisting of: N; C-H; C-R^d, wherein R^d is selected from the group consisting of halogen; alkoxy; C1-3 alkylhydroxy; C1-3 haloalkyl; C2-5 alkyl alkoxy; C2-5 alkyl nitrile.

5. The compound of Claim 4, wherein Ring Z is:



6. The compound of Claim 2 or Claim 3, wherein G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N, C-F and C-H;

R1 is selected from the group consisting of: hydrogen, Me; Et; OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring;

R3 is hydrogen or halogen;

R4 is selected from the group consisting of: hydrogen; Me, Et, CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; OCF_3; CN; Cl and F; and

wherein:

R8 and R9 are each independently selected from the group consisting of: hydrogen; Me; Et; CH_2OH; CHMeOH; CMe_2OH; CH_2OMe; CH_2F and halogen;

R10 and R11 are each independently selected from the group consisting of: hydrogen; Me, Et, CH_2OH, CHMeOH, CMe_2OH, CH_2OMe, CH_2F CHF2; CH_2CF_3 and CH_2-heteroaryl;

R12 is selected from the group consisting of: hydrogen and Me;

R13 is selected from the group consisting of: hydrogen and Me;

R21 is selected from the group consisting of: hydrogen; and Me; or

wherein:

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R21, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

7. The compound of Claim 6, wherein:

a) one of R8 and R9 is joined to one of R10 and R11 to form a [6,3]-, [6,4]-, [6,5]-, [6,7]- or [6,8]-bicyclic structure;

b) one of R8 and R9 is joined to R13 to form a [6,5,5]-, [6,6,6]-, [6,7,7]- or [6,8,8]-, bridged structure;

c) one of R10 and R11 is joined to R13 to form a [6,6,4]-, [6,7,5]- or [6,8,6]-, bridged structure;

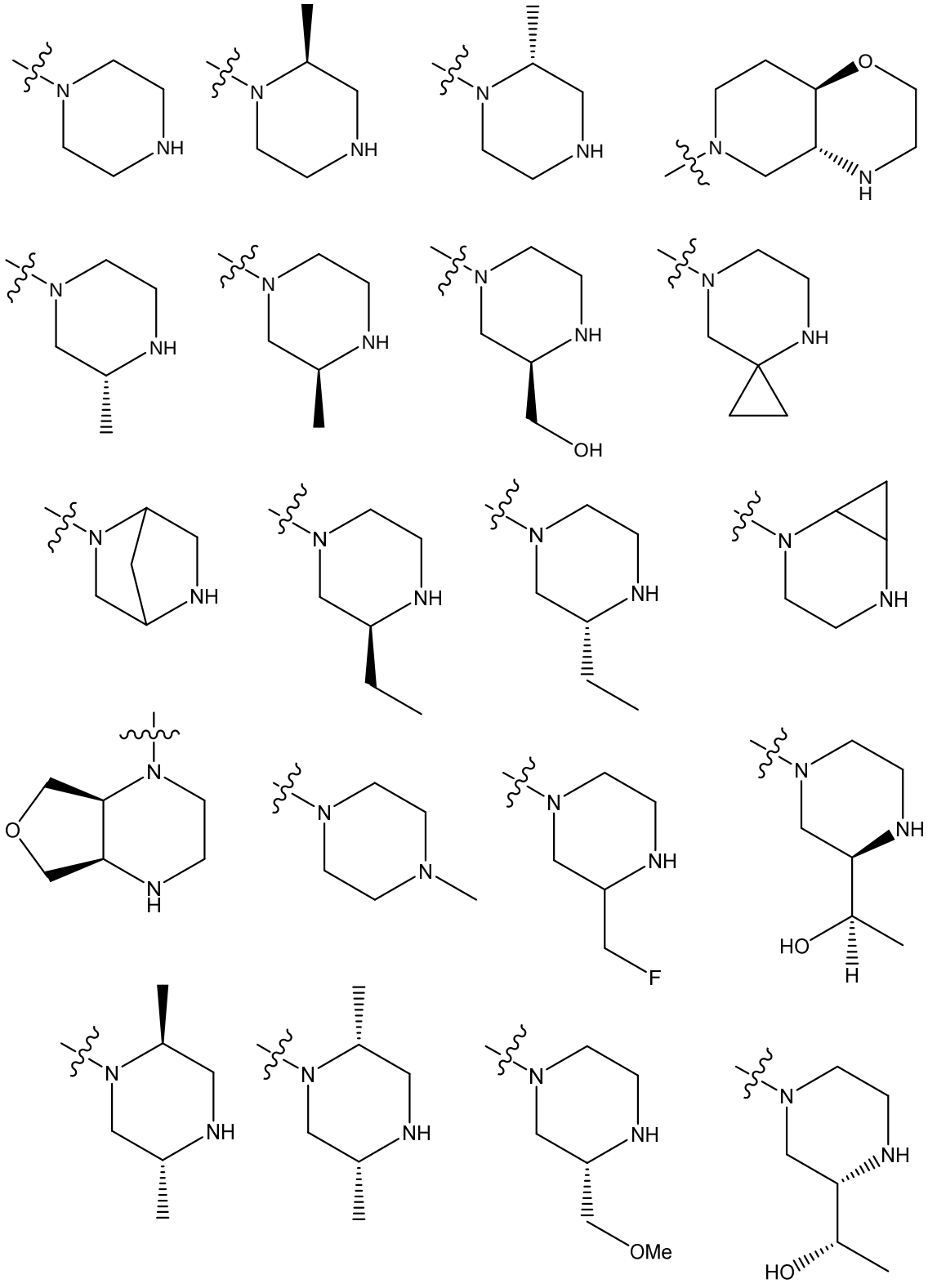
d) one of R10 and R11 may be joined to R21 to form a [6,5,5]-, [6,6,6]-, [6,7,7]-, [6,8,8]-, bridged structure;

e) one of R8 and R9 may be joined to R21 to form a [6,6,4]-, [6,7,5]-, [6,8,6]-, bridged structure;

f) R8 is joined to R9 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure; or

g) R10 is joined to R11 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure.

8. The compound of any one of Claims 1, 2 and 6, wherein Ring Z is selected from the group consisting of:



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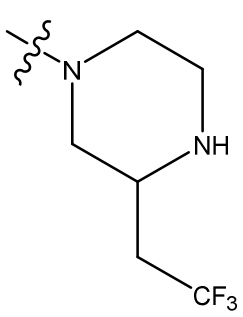
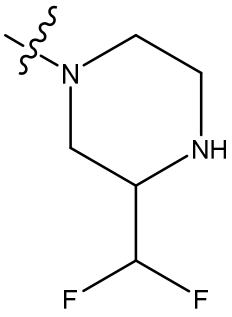
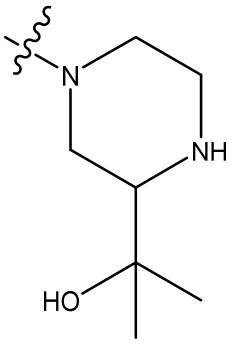
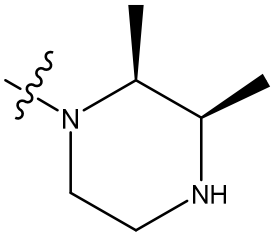
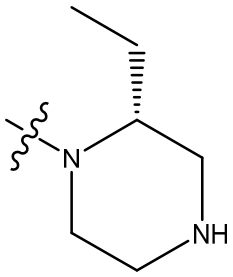
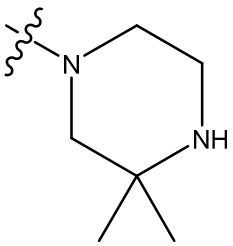

N
NH
CF3

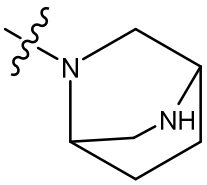

N
NH
F
F

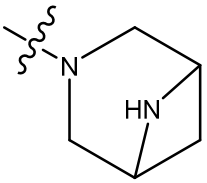

N
NH
HO

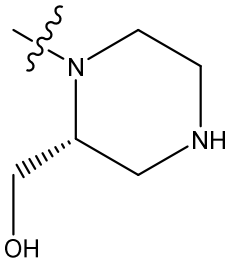

N
NH

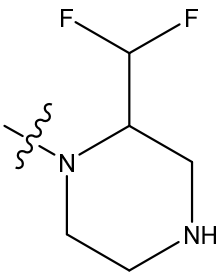

N
NH

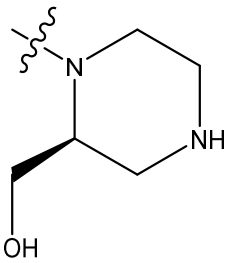

N
NH

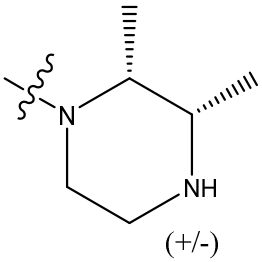

N
NH

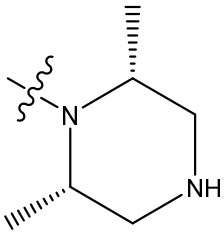

N
HN

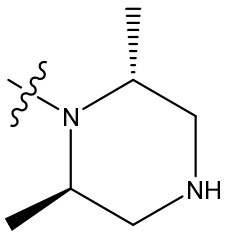

N
NH
OH

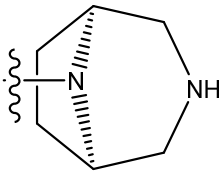

F
F
N
NH

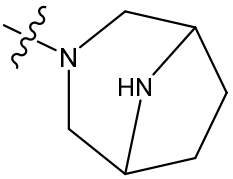

N
NH
OH


N
NH
(+/-)


N
NH


N
NH


N
NH


N
HN

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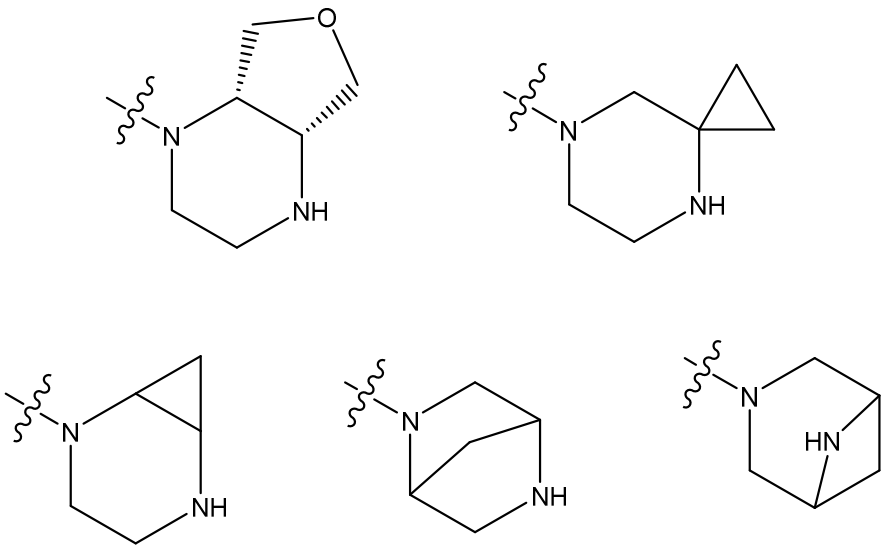
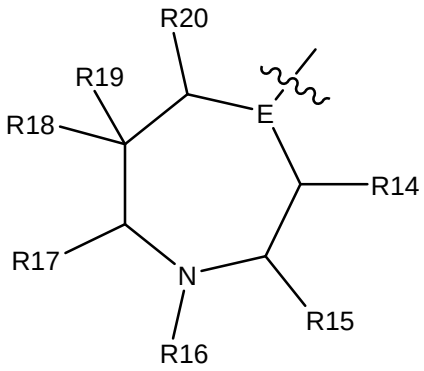
9. The compound of any one of Claims 1, 2, 6 and 8, wherein Ring Z is selected from the group consisting of:



10. The compound of Claim 2 or Claim 3, wherein G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N; C-H and C-F;

R1 is selected from the group consisting of: hydrogen; Me; Et, OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered carbocyclic or heterocyclic spiro ring;

R3 is selected from the group consisting of: hydrogen and F;

R4 is selected from the group consisting of: Me; Et; CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; CN; Cl and F;

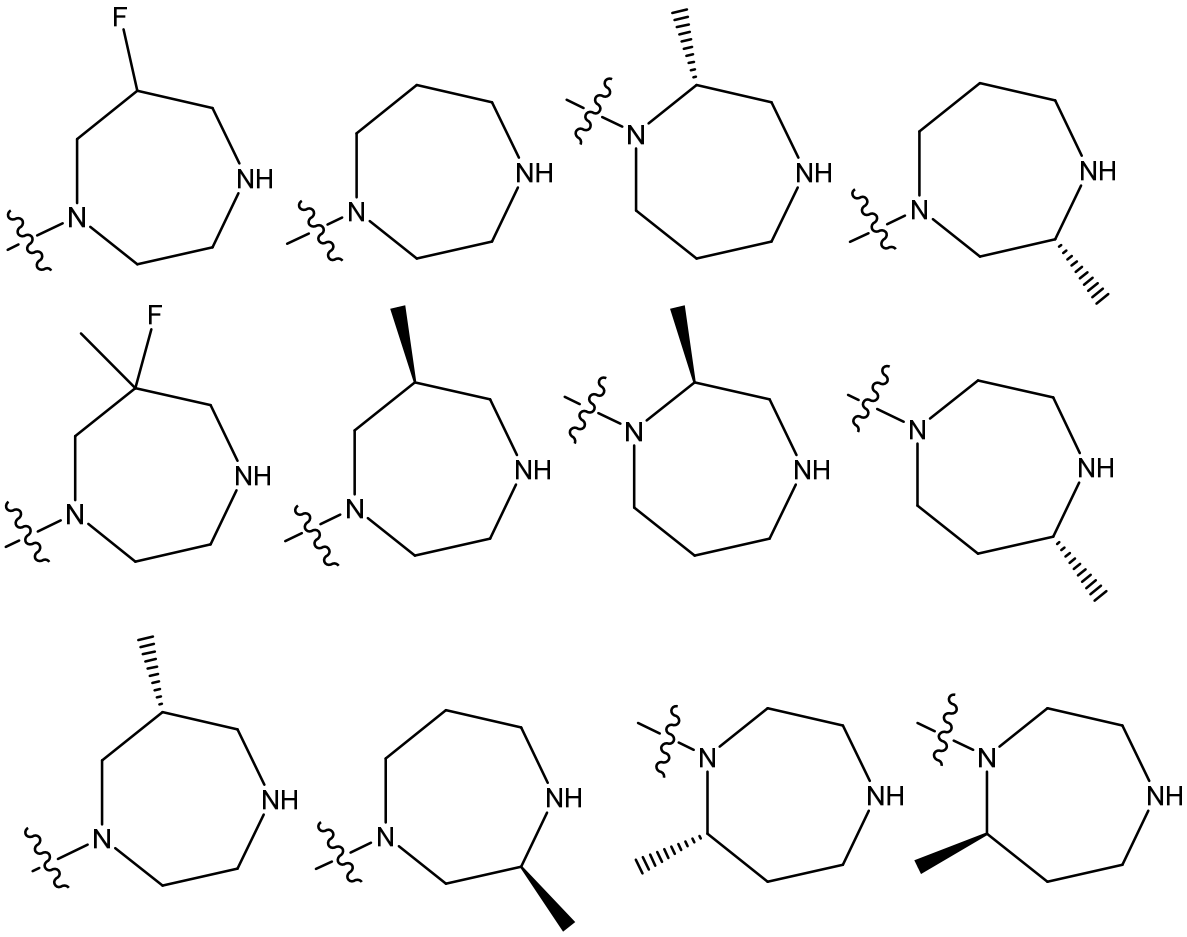
R14, R15, R17, R18, R19 and R20 is each independently selected from the group consisting of: hydrogen, Me and F.

R16 is selected from the group consisting of: hydrogen and Me.

11. The compound of Claim 10, wherein:

a) each of R14, R15, R16, R17, R18, R19 and R20 are hydrogen;
b) when one of R14, R15, R17, R18 and R20 is Me, R16 and R19 are hydrogen;
c) when R18 is F, R14, R15, R16, R17, R19 and R20 are hydrogen;
d) when R18 is F and R19 is Me, R14, R15, R16, R17 and R19 are hydrogen;
e) wherein R18 and R19 are both F and R14, R15, R17 and R20 are hydrogen;
f) when E is C-H, and R14 or R20 is F.

12. The compound of Claim 1 or Claim 10, wherein Ring Z is selected from the group consisting of:



13. The compound of any one of Claims 1 to 12, wherein when G is N-H, B is N.

14. A compound according to Table 1, or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof.

15. A pharmaceutical composition comprising one or more compound of any of Claims 1 to 14 or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, and one or more pharmaceutically acceptable carrier.

16. The compound of any of Claims 1 to 14 or the pharmaceutical composition of Claim 15 for use in the treatment of a disorder or disease selected from an autoimmune disorder and/or

inflammatory disease and/or oncologic disease and/or cancer and/or HIV infection and replication.

17. The compound or pharmaceutical composition for use according to Claim 16, wherein the disorder or disease is selected from the group consisting of: rheumatoid arthritis, multiple sclerosis, psoriasis and atopic dermatitis.

18. The compound or pharmaceutical composition for use according to Claim 16 or Claim 17, wherein the compound is an inhibitor of PKC-theta.

19. The compound or pharmaceutical composition for use according to any of Claims 16 to 18, wherein the compound is to be administered orally; topically; by inhalation; by intranasal administration; or systemically by intravenous, intraperitoneal, subcutaneous, or intramuscular injection.

20. The compound or pharmaceutical composition for use according to any of Claims 16 to 19, wherein one or more compound according to any one of Claims 1 to 14 is to be administered optionally in combination with one or more additional therapeutic agent.

21. The compound or pharmaceutical composition for use according to Claim 20, wherein the one or more compound according to any one of Claims 1 to 14 is to be administered simultaneously, sequentially or separately from the one or more additional therapeutic agent.

22. The compound or pharmaceutical composition for use according to any of Claims 16 to 21, wherein an effective amount of the compound according to any one of Claims 1 to 14 is to be administered to a subject, wherein the effective amount is between about 5 nM and about 10 µM in the blood of the subject.

23. Use of the compound of any of Claims 1 to 14 or the pharmaceutical composition of Claim 15 in the manufacture of a medicament for the treatment of a disorder or disease selected from an autoimmune disorder and/or inflammatory disease and/or oncologic disease and/or cancer and/or HIV infection and replication.

24. The use according to Claim 23, wherein the disorder or disease is selected from the group consisting of: rheumatoid arthritis, multiple sclerosis, psoriasis and atopic dermatitis.

25. The use according to Claim 23 or Claim 24, wherein the compound is an inhibitor of PKC-theta.

26. The use according to any of Claims 23 to 25, wherein the compound is to be administered orally; topically; by inhalation; by intranasal administration; or systemically by intravenous, intraperitoneal, subcutaneous, or intramuscular injection.

27. The use according to any of Claims 23 to 26, wherein one or more compound according to any one of Claims 1 to 14 is to be administered optionally in combination with one or more additional therapeutic agent.

28. The use according to Claim 27, wherein the one or more compound according to any one of Claims 1 to 14 is to be administered simultaneously, sequentially or separately from the one or more additional therapeutic agent.

29. The use according to any of Claims 23 to 28, wherein an effective amount of the compound according to any one of Claims 1 to 14 is to be administered to a subject, wherein the effective amount is between about 5 nM and about 10 µM in the blood of the subject.

30. The compound of any of Claims 1 to 14 or the pharmaceutical composition of Claim 15 for use in therapy.