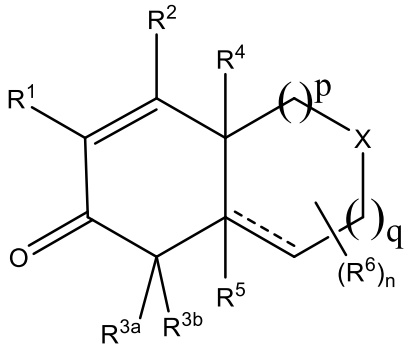
CLAIMS

1. A compound represented by Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein

R^1 is –CN, -C(O)R^a, $CH_3S(O)_2$- or C_{1-8}alkyl substituted with one or more fluorine atoms;

R^a is H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, -OR^{11}, -SR^{14}, -$N(R^{12})_2$, -$NR^{13}OR^{13}$, -$NR^{13}S(O)_2R^{13}$, -$NR^{13}C(O)R^{13}$, -$N(R^{13})N(R^{13})_2$, -$N(R^{13})C(O)OR^{13}$ or -$N(R^{13})C(O)N(R^{13})_2$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl, and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

R^2 is H, halo, -NO_2, -CN, -N_3, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, -C(O)R^{13}, -C(S)R^{13}, -C(O)OR^{13}, -C(S)SR^{13}, -C(O)SR^{13}, -C(S)OR^{13}, -SC(O)R^{13}, -OC(S)R^{13}, -SC(S)R^{13}, -C(O)$N(R^{13})_2$, -OR^{11}, -SR^{14}, -$N(R^{12})_2$, -$N(R^{13})OR^{13}$, -$N(R^{13})S(O)_2R^{13}$, -$N(R^{13})C(O)R^{13}$, -$N(R^{13})N(R^{13})_2$, -$N(R^{13})C(O)OR^{13}$, -$N(R^{13})C(O)N(R^{13})_2$, -$S(O)_2R^{13}$, -S(O)R^{13}, -$S(O)N(R^{13})_2$, -$S(O)_2N(R^{13})_2$, -$N^+(R^{13})_3$, -$S^+(R^{13})_2$ or -$Si(R^{13})_3$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

R^{3a} is H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, -C(O)R^{13}, -C(O)OR^{13}, -C(O)$N(R^{13})_2$, -OR^{11}, -$N(R^{12})_2$, -$N(R^{13})OR^{13}$, -$N(R^{13})S(O)_2R^{13}$, -$N(R^{13})C(O)R^{13}$, -$N(R^{13})N(R^{13})_2$, -$N(R^{13})C(O)OR^{13}$, -$N(R^{13})C(O)N(R^{13})_2$, -S(O)R^{13}, -$S(O)N(R^{13})_2$ or -$S(O)_2N(R^{13})_2$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21}; and

R^{3b} is C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^{13})_2$, $-OR^{11}$, $-N(R^{12})_2$, $-N(R^{13})OR^{13}$, $-N(R^{13})S(O)_2R^{13}$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})N(R^{13})_2$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-S(O)R^{13}$, $-S(O)N(R^{13})_2$ or $-S(O)_2N(R^{13})_2$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21}; or

R^{3a} and R^{3b} are taken together and are C_{2-12}alkylene, C_{2-12}alkenylene or C_{2-12}alkynylene; wherein the C_{2-12}alkylene, C_{2-12}alkenylene, C_{2-12}alkynylene and 3-6-membered carbocyclyl are each optionally substituted with one or more R^{21};

R^4 is H, halo, $-NO_2$, -CN, $-N_3$, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-C(O)OR^{13}$, $-C(S)SR^{13}$, $-C(O)SR^{13}$, $-C(S)OR^{13}$, $-SC(O)R^{13}$, $-OC(S)R^{13}$, $-SC(S)R^{13}$, $-C(O)N(R^{13})_2$, $-OR^{11}$, $-SR^{14}$, $-N(R^{12})_2$, $-N(R^{13})OR^{13}$, $-N(R^{13})S(O)_2R^{13}$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})N(R^{13})_2$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-S(O)_2R^{13}$, $-S(O)R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-N^+(R^{13})_3$, $-S^+(R^{13})_2$ or $-Si(R^{13})_3$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

"------" is either a single bond or a double bond, wherein when "------" is a double bond, then R^5 is absent; and when "------" is a single bond, then

R^5 is H, halo, $-NO_2$, -CN, $-N_3$, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-C(O)OR^{13}$, $-C(S)SR^{13}$, $-C(O)SR^{13}$, $-C(S)OR^{13}$, $-SC(O)R^{13}$, $-OC(S)R^{13}$, $-SC(S)R^{13}$, $-C(O)N(R^{13})_2$, $-OR^{11}$, $-SR^{14}$, $-N(R^{12})_2$, $-N(R^{13})OR^{13}$, $-N(R^{13})S(O)_2R^{13}$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})N(R^{13})_2$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-S(O)_2R^{13}$, $-S(O)R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-N^+(R^{13})_3$, $-S^+(R^{13})_2$ or $-Si(R^{13})_3$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21}; or

R^5 and R^{3b} are taken together with the carbons to which they each are attached form a 3-6-membered carbocyclyl, wherein the 3-6-membered carbocyclyl is optionally substituted with one or more R^{21};

R^6, in each occurrence, is independently halo, $-NO_2$, -CN, $-N_3$, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-C(O)OR^{13}$, $-C(S)SR^{13}$, $-C(O)SR^{13}$, $-C(S)OR^{13}$, $-SC(O)R^{13}$, $-OC(S)R^{13}$, $-SC(S)R^{13}$, $-C(O)N(R^{13})_2$, $-OR^{11}$, $-SR^{14}$, $-N(R^{12})_2$, $-N(R^{13})OR^{13}$, $-N(R^{13})S(O)_2R^{13}$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})N(R^{13})_2$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-S(O)_2R^{13}$, $-S(O)R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-N^+(R^{13})_3$, $-S^+(R^{13})_2$ or $-Si(R^{13})_3$; or two R^6 attached to the same ring carbon to form an oxo, $=NR^{14}$ or C_{1-12}alkylidene, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl, 3 to 12-membered heterocyclyl and C_{1-12}alkylidene are each optionally substituted with one or more R^{21};

X is NR^b or O;

R^b is H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$ or $-S(O)_2NR^cR^c$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

R^c, in each occurrence, is independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl and a 3 to 12-membered heterocyclyl, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

R^{11}, in each occurrence, is independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, C_{1-12}acyl and $-Si(R^{13})_3$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl, 3 to 12-membered heterocyclyl, and C_{1-12}acyl are each optionally substituted with one or more R^{21};

R^{12}, in each occurrence, is independently selected from H, C_{1-12}alkyl, C_{1-12}alkoxy, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl and $-Si(R^{13})_3$, wherein the C_{1-12}alkyl, C_{1-12}alkoxy, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21};

R^{13}, in each occurrence, is independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, and a 3 to 12-membered heterocyclyl, wherein the C_{1-}

$_{12}$alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are optionally substituted with one or more R^{21};

R^{14}, in each occurrence, is independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl and C_{1-12}acyl, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl, 3 to 12-membered heterocyclyl and C_{1-12}acyl are each optionally substituted with one or more R^{21};

R^{21}, in each occurrence, is independently selected from halo, -OH, $-S(O)_2R^{16}$, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{1-12}alkoxy, a 3 to 12-membered carbocyclyl and a 3 to 12-membered heterocyclyl, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{1-12}alkoxy, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkyl and C_{1-4}alkoxy;

R^{16}, in each occurrence, is independently selected from H or C_{1-12}alkyl;

n is 0 or an integer from 1 to 8;

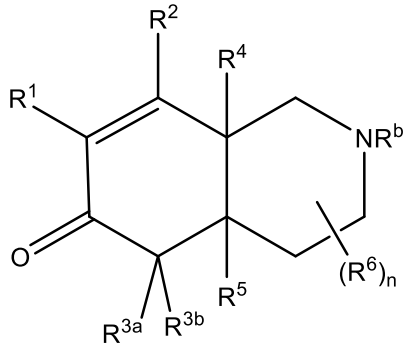
p is 0, 1 or 2; and

q is 1, 2 or 3,

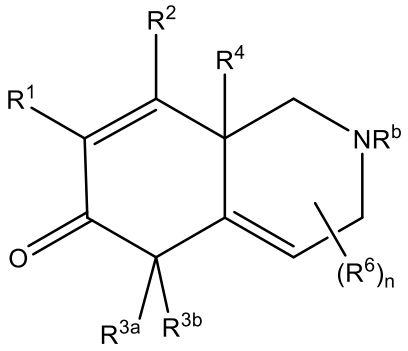
provided that the sum of p and q is not 4 or 5.

2. The compound of claim 1, wherein the compound is represented by:

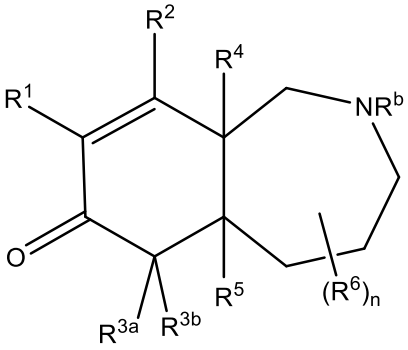
Formula II:



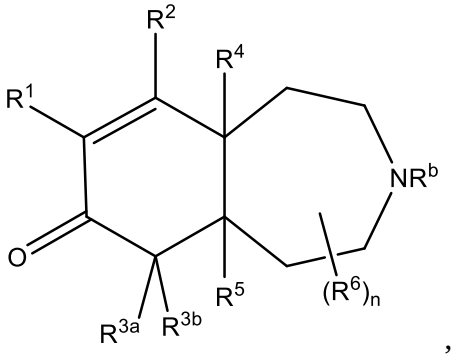
or Formula III:



or Formula IV:



or Formula V:

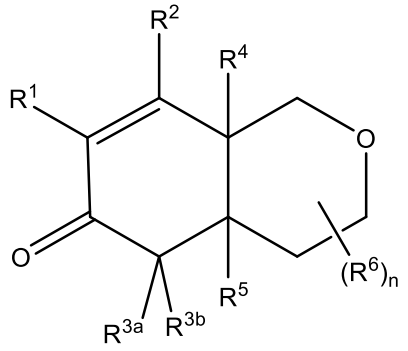

,

or a pharmaceutically acceptable salt thereof.

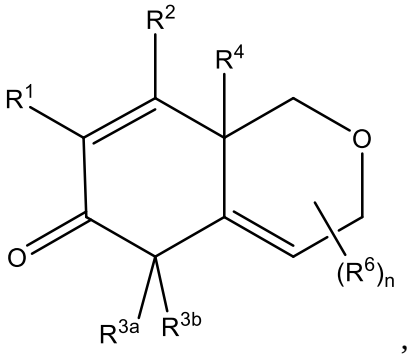
3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R^b is H, C_{1-12}alkyl, a 6 to 12-membered aryl, a 3-12-membered heterocyclyl, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^c$, -$S(O)_2R^c$, -$S(O)_2OR^c$ or -$S(O)_2NR^cR^c$, wherein R^c, in each occurrence, is independently H, C_{1-6}alkyl, a 3 to 8-membered cycloalkyl, a 3 to 8-membered heterocyclyl or a 6 to 12-membered aryl, wherein the alkyl, cycloalkyl, heterocyclyl and aryl, in each occurrence, in R^b or R^c are optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-

membered heteroaryl, wherein the heterocyclyl and heteroaryl each comprise 1 to 3 heteroatoms, wherein the heteroatoms are selected from the group consisting of N, S and O.

4. The compound of claim 1, wherein the compound is represented by:
Formula VI:



or Formula VII:



,

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein
R^1 is –CN, -CF_3 or -C(O)R^a; and/or
R^2 is H, -OH, halo, C_1-$_{12}$alkyl or C_1-$_{12}$alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein either:

(i) R^{3a} is H; and R^{3b} is C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 6 to 12-membered aryl, a 5 to 12-membered heteroaryl, $-C(O)R^{13}$, $-OR^{11}$, $-N(R^{12})_2$ or $-N(R^{13})C(O)R^{13}$, wherein R^{11} is independently H, C_{1-12}alkyl, C_{1-12}acyl, a 6 to 12-membered aryl or a 5 to 12-membered heteroaryl; and R^{12} and R^{13}, in each occurrence, are independently H, C_{1-12}alkyl, a 6 to 12-membered aryl or a 5 to 12-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl and acyl, in each occurrence, in R^{11}, R^{12} and R^{13} are optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl; or

(ii) R^{3a} is C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, a 3 to 12-membered carbocyclyl, a 3 to 12-membered heterocyclyl, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^{13})_2$, $-OR^{11}$, $-N(R^{12})_2$, $-N(R^{13})OR^{13}$, $-N(R^{13})S(O)_2R^{13}$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})N(R^{13})_2$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-S(O)R^{13}$, $-S(O)N(R^{13})_2$ or $-S(O)_2N(R^{13})_2$, wherein the C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, 3 to 12-membered carbocyclyl and 3 to 12-membered heterocyclyl are each optionally substituted with one or more R^{21}; or

(iii) R^{3a} and R^{3b} are taken together and are C_{2-12}alkylene, C_{2-12}alkenylene or C_{2-12}alkynylene.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^4 is H, -OH, halo, C_{1-12}alkyl, C_{1-12}alkoxy or 6 to 12-membered aryl, wherein the alkyl, alkoxy and aryl are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl; and/or

(ii) R^5 is H, -OH, halo, C_{1-12}alkyl or C_{1-12}alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl; and/or

(iii) R^6 is -OH, halo, C_{1-12}alkyl or C_{1-12}alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl.

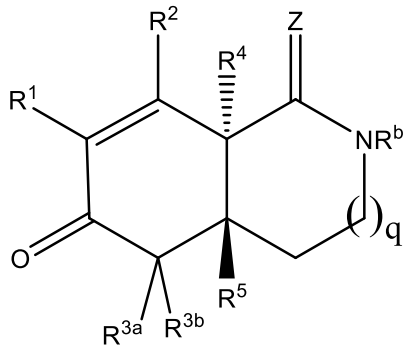
8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein:

(i) n is 1 or 2; or

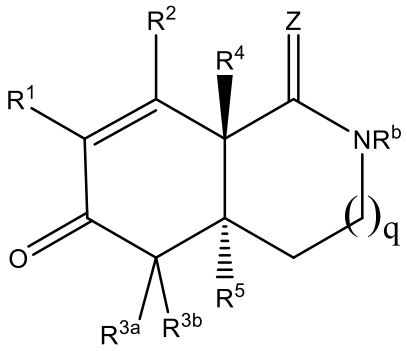
(ii) wherein n is 2; and two R^6 are attached to the same ring carbon to form an oxo, $=NR^{14}$ or $C_{1\text{-}12}$alkylidene; or

(iii) n is 2 and the compound is represented by:

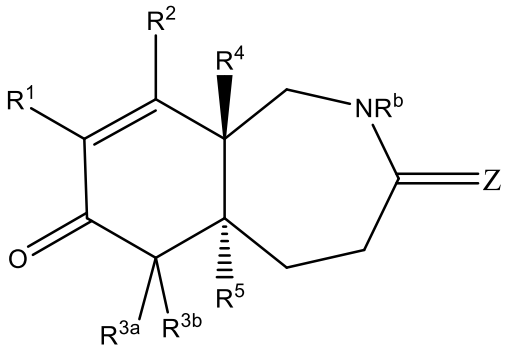
Formula VIII(A):



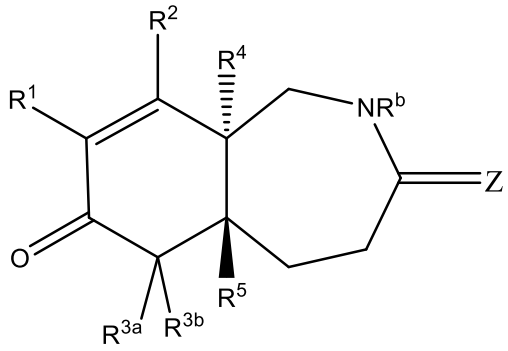
or Formula VIII(B):



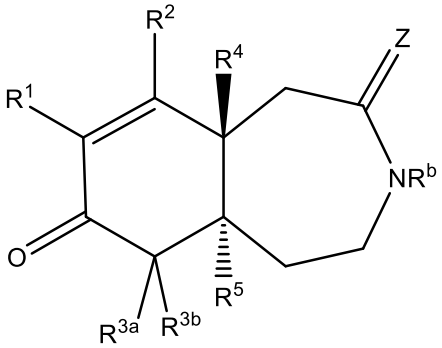
or Formula IX(A):



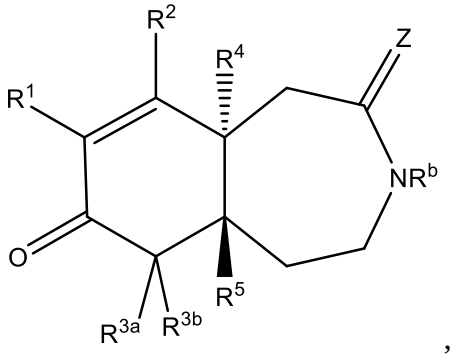
or Formula IX(B):



or Formula X(A):



or Formula X(B):


,

or a pharmaceutically acceptable salt thereof, wherein Z is:

(a) O, NR^{22} or $C(R^{22})_2$, wherein R^{22}, in each occurrence, is independently H or a $C_{1\text{-}4}$alkyl optionally substituted with 1 to 3 groups selected from halo, -OH and $C_{1\text{-}4}$alkoxy; or

(b) Z is O; or

(iv) n is 0.

9. The compound of any one of claims 1, 2 or 4, or a pharmaceutically acceptable salt thereof, wherein

R^1 is –CN, -CF_3 or -C(O)R^a;

R^2 is H, -OH, halo, C_{1-12}alkyl or C_{1-12}alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl;

R^{3a} is H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, -C(O)R^{13}, -OR^{11}, -N(R^{12})$_2$ or -N(R^{13})C(O)R^{13}; and R^{3b} is C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, -C(O)R^{13}, -OR^{11}, -N(R^{12})$_2$ or -N(R^{13})C(O)R^{13}, wherein R^{11} to R^{13} are each independently H or C_{1-4}alkyl; or R^{3a} and R^{3b} taken together with the carbon, to which they are both attached to, form a C_{3-8} membered non-aromatic ring;

R^4 is H, -OH, halo, C_{1-12}alkyl, C_{1-12}alkoxy or 6 to 12-membered aryl, wherein the alkyl, alkoxy and aryl are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl;

"------" is a single bond;

R^5 is H, -OH, halo, C_{1-12}alkyl or C_{1-12}alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl;

R^b is H, C_{1-12}alkyl, a 6 to 12-membered aryl, a 3-12-membered heterocyclyl, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^c, -$S(O)_2R^c$, -$S(O)_2OR^c$ or -$S(O)_2NR^cR^c$, wherein R^c, in each occurrence, is independently H, C_{1-6}alkyl, a 3 to 8-membered cycloalkyl, a 3 to 8-membered heterocyclyl or a 6 to 12-membered aryl, wherein the alkyl, cycloalkyl, heterocyclyl and aryl, in each occurrence, in R^b or R^c are optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl, wherein the heterocyclyl comprises 1 to 3 heteroatoms, wherein the heteroatoms are selected from the group consisting of N, S and O; and

n is 0 or 2, wherein, when n is 2, two R^6 are attached to the same ring carbon to form an oxo, =NR^{14} or C_{1-12}alkylidene.

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

R^1 is –CN, $-CF_3$ or $-C(O)R^a$;

R^2 is H, -OH, halo, C_{1-12}alkyl or C_{1-12}alkoxy, wherein the alkyl and alkoxy are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl;

R^{3a} is H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, $-C(O)R^{13}$, $-OR^{11}$, $-N(R^{12})_2$ or $-N(R^{13})C(O)R^{13}$; and R^{3b} is C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, $-C(O)R^{13}$, $-OR^{11}$, $-N(R^{12})_2$ or $-N(R^{13})C(O)R^{13}$, wherein R^{11} to R^{13} are each independently H or C_{1-4}alkyl; or R^{3a} and R^{3b} taken together with the carbon, to which they are both attached to, form a C_{3-8} membered non-aromatic ring;

R^4 is H, -OH, halo, C_{1-12}alkyl, C_{1-12}alkoxy or 6 to 12-membered aryl, wherein the alkyl, alkoxy and aryl are each optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl;

"------" is a double bond;

R^b is H, C_{1-12}alkyl, a 6 to 12-membered aryl, a 3-12-membered heterocyclyl, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$ or $-S(O)_2NR^cR^c$, wherein R^c, in each occurrence, is independently H, C_{1-6}alkyl, a 3 to 8-membered cycloalkyl, a 3 to 8-membered heterocyclyl or a 6 to 12-membered aryl, wherein the alkyl, cycloalkyl, heterocyclyl and aryl, in each occurrence, in R^b or R^c are optionally substituted with 1 to 3 groups selected from halo, -OH, C_{1-4}alkoxy, a 6 to 12-membered aryl and a 5 to 12-membered heteroaryl, wherein the heterocyclyl and heteroaryl each comprise 1 to 3 heteroatoms, wherein the heteroatoms are selected from the group consisting of N, S and O; and

n is 0.

11. The compound of claim 1 selected from the group consisting of:

(4aS,5S,8aR)-2-benzyl-5-methyl-1,6-dioxo-8a-phenyl-1,2,3,4,4a,5,6,8a-octahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-benzyl-5-methyl-1,6-dioxo-8a-phenyl-1,2,3,4,4a,5,6,8a-octahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-1,6-dioxo-8a-phenyl-2-(3-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-1,6-dioxo-8a-phenyl-2-(3-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aR)-2-(2-hydroxyethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aS)-2-(2-hydroxyethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5R,8aR)-5-methyl-1,6-dioxo-8a-phenyl-2-(2-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5S,8aS)-5-methyl-1,6-dioxo-8a-phenyl-2-(2-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-cyclobutyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-cyclobutyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aR)-5-methyl-2-[(1-methylpyrazol-4-yl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aS)-5-methyl-2-[(1-methylpyrazol-4-yl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-[(3-methoxyphenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-[(3-methoxyphenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-[(3-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-[(3-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-[(4-methoxyphenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-[(4-methoxyphenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aS)-2-isopropyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aR)-2-isopropyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-(cyclopropylmethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-(cyclopropylmethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-[(4-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-[(4-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-(2,2-difluoroethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-(2,2-difluoroethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-[(2-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-[(2-fluorophenyl)methyl]-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2-methoxyethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aR,8aR)-2-(2-methoxyethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-(2-methoxyethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-(2-methoxyethyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aS)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aR,8aR)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aR,8aR)-5,5,8a-trimethyl-2-(2-methylpyrimidin-4-yl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(5aR,9aS)-3-acetyl-5a,9,9-trimethyl-8-oxo-2,4,5,9a-tetrahydro-1H-3-benzazepine-7-carbonitrile;

(4aR,8aR)-5,5,8a-trimethyl-2-(6-methylpyrimidin-4-yl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile hydrochloride;

(5aS,9aR)-2-(2,2-difluoroethyl)-6,6,9a-trimethyl-7-oxo-3,4,5,5a-tetrahydro-1H-2-benzazepine-8-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-2-(2-methylpyrimidin-5-yl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-(2,2,2-trifluoroacetyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-2-ethyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-ethyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(4aR,8aS)-2-ethyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aS,8aR)-2-ethyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aR,5S,8aR)-2-acetyl-5-ethyl-5,8a-dimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(5R,8aR)-2-acetyl-5-benzyl-5,8a-dimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(5S,8aR)-2-acetyl-5-benzyl-5,8a-dimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(5R,8aR)-2-acetyl-5-ethyl-5,8a-dimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(5S,8aR)-2-acetyl-5-ethyl-5,8a-dimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(4aS,5R,8aR)-2,5-dimethyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5S,8aS)-2,5-dimethyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(4aS,5R,8aR)-2-ethyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5S,8aS)-2-ethyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-[(2S)-2-fluoropropanoyl]-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-[(2R)-2-fluoropropanoyl]-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2,2-difluoroethyl)-5,5-dimethyl-6-oxo-8a-phenyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(2,2-difluoroethyl)-5,5-dimethyl-6-oxo-8a-phenyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

methyl (4aS,8aR)-7-cyano-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-2-carboxylate;

(4aS,8aR)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

tert-butyl (4aR,8aR)-7-cyano-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-2-carboxylate;

(4aS,8aR)-2-acetyl-5,5-dimethyl-6-oxo-8a-phenyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-acetyl-5,5-dimethyl-6-oxo-8a-phenyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydro-2H-isoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydro-2H-isoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-pyrazin-2-yl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2,2-difluoroethyl)-8a-ethyl-5,5-dimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(2,2-difluoroethyl)-8a-ethyl-5,5-dimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-8a-ethyl-5,5-dimethyl-6-oxo-2-pyrimidin-2-yl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-8a-ethyl-5,5-dimethyl-6-oxo-2-pyrimidin-2-yl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-acetyl-8a-ethyl-5,5-dimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-acetyl-8a-ethyl-5,5-dimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aR)-2-(2-methoxyethyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aR)-5,5,8a-trimethyl-2-(2-methylsulfonylethyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(5aS,9aR)-2-acetyl-6,6,9a-trimethyl-7-oxo-3,4,5,5a-tetrahydro-1H-2-benzazepine-8-carbonitrile;

(5aS,9aR)-6,6,9a-trimethyl-3,7-dioxo-2,4,5,5a-tetrahydro-1H-2-benzazepine-8-carbonitrile;

(5aR,9aS)-5a,9,9-trimethyl-4,8-dioxo-2,3,5,9a-tetrahydro-1H-3-benzazepine-7-carbonitrile;

(5aS,9aS)-1,6,6,9a-tetramethyl-2,7-dioxo-3,4,5,5a-tetrahydro-1-benzazepine-8-carbonitrile;

(5aS,9aS)-6,6,9a-trimethyl-2,7-dioxo-3,4,5,5a-tetrahydro-1H-1-benzazepine-8-carbonitrile;

(3R,4aS,8aR)-2-acetyl-3,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(3S,4aR,8aS)-2-acetyl-3,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2,5,5,8a-tetramethyl-3,6-dioxo-4,4a-dihydro-1H-isoquinoline-7-carbonitrile;

(4aS,8aR)-2,5,5,8a-tetramethyl-3,6-dioxo-4,4a-dihydro-1H-isoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-3,6-dioxo-1,2,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-3,6-dioxo-1,2,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,7aR,8aR)-3-ethyl-7a-methyl-4,7-dioxo-4a-phenyl-2,8-dihydro-1H-cyclopropa[e]isoquinoline-6-carbonitrile;

(4aS,7aS,8aS)-3-ethyl-7a-methyl-4,7-dioxo-4a-phenyl-2,8-dihydro-1H-cyclopropa[e]isoquinoline-6-carbonitrile;

(4aR,8aR)-2-ethyl-5,5-dimethyl-8a-phenyl-7-(trifluoromethyl)-4,4a-dihydro-3H-isoquinoline-1,6-dione;

(4aS,8aS)-2-ethyl-5,5-dimethyl-8a-phenyl-7-(trifluoromethyl)-4,4a-dihydro-3H-isoquinoline-1,6-dione;

(4aS,8aR)-2-acetyl-5,5,8a-trimethyl-7-(trifluoromethyl)-1,3,4,4a-tetrahydroisoquinolin-6-one;

(4aR,8aS)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carboxamide;

(4aS,8aR)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carboxamide;

(8aR)-8a-(4-fluorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aS)-8a-(4-fluorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-(4-chlorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-(4-chlorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aS)-8a-(3-fluorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-(3-fluorophenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-(4-methoxyphenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-(4-methoxyphenyl)-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-8a-benzyl-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aS)-8a-benzyl-2,5,5-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(4aS,8aS)-2-acetyl-5,5,8a-trimethyl-7-methylsulfonyl-1,3,4,4a-tetrahydroisoquinolin-6-one;

(8aS)-5,5-dimethyl-2-(1-methylpyrazol-3-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(1-methylpyrazol-3-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-2-(1-methylpyrazol-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(1-methylpyrazol-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-2-(2-methylpyrazol-3-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(2-methylpyrazol-3-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-2-(1-methylimidazol-2-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(1-methylimidazol-2-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-2-(6-methylpyrimidin-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(6-methylpyrimidin-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-2-(2-methylpyrimidin-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-2-(2-methylpyrimidin-4-yl)-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyridazin-4-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyridazin-4-yl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-5-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-5-yl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyridazin-3-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyridazin-3-yl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrazin-2-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrazin-2-yl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-4-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-4-yl-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(2-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(2-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(3-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(3-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(4-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(4-pyridyl)-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-2-yl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-pyrimidin-2-yl-3H-isoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-(4-methoxyphenyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-(4-methoxyphenyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-(4-fluorophenyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-(4-fluorophenyl)-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-1,6-dioxo-8a-phenyl-2-pyrimidin-4-yl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-1,6-dioxo-8a-phenyl-2-pyrimidin-4-yl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5R,8aR)-5-methyl-1,6-dioxo-2,8a-diphenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5S,8aS)-5-methyl-1,6-dioxo-2,8a-diphenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-ethyl-5,8a-dimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-ethyl-5,8a-dimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2,5,8a-trimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2,5,8a-trimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aR)-2-isopropyl-5,5,8a-trimethyl-1,6-dioxo-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aS,8aS)-2-isopropyl-5,5,8a-trimethyl-1,6-dioxo-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aS,8aS)-2,5,5,8a-tetramethyl-1,6-dioxo-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(4aR,8aR)-2,5,5,8a-tetramethyl-1,6-dioxo-4,4a-dihydro-3H-isoquinoline-7-carbonitrile;

(8aR)-2-ethyl-5,5,8a-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aS)-2-ethyl-5,5,8a-trimethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aR)-2-cyclobutyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-cyclobutyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(3-pyridylmethyl)-3H-isoquinoline-7-carbonitrile;

(8aS)-5,5-dimethyl-1,6-dioxo-8a-phenyl-2-(3-pyridylmethyl)-3H-isoquinoline-7-carbonitrile;

(8aR)-2-cyclopropyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-cyclopropyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-isopropyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-isopropyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-cyclopentyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-cyclopentyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-isobutyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-isobutyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-benzyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-benzyl-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-(2-methoxyethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-(2-methoxyethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aR)-2-(cyclopropylmethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(8aS)-2-(cyclopropylmethyl)-5,5-dimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-benzyl-5,8a-dimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-benzyl-5,8a-dimethyl-1,6-dioxo-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-2,5,5,8a-tetramethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(8aS)-2,5,5,8a-tetramethyl-1,6-dioxo-3H-isoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-2-[(2-methyl-4-pyridyl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-2-[(2-methyl-4-pyridyl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-2-[(5-methylisoxazol-3-yl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-2-[(5-methylisoxazol-3-yl)methyl]-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aR,5R,8aS)-5-methyl-1,6-dioxo-8a-phenyl-2-(4-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-5-methyl-1,6-dioxo-8a-phenyl-2-(4-pyridylmethyl)-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(5aS,9aR)-5a,9,9-trimethyl-4,8-dioxo-2,3,4,5,5a,8,9,9a-octahydro-1H-benzo[d]azepine-7-carbonitrile;

(5aR,9aS)-6,6,9a-trimethyl-3,7-dioxo-2,3,4,5,5a,6,7,9a-octahydro-1H-benzo[c]azepine-8-carbonitrile;

(5aR,9aS)-2-acetyl-6,6,9a-trimethyl-7-oxo-2,3,4,5,5a,6,7,9a-octahydro-1H-benzo[c]azepine-8-carbonitrile;

(4aS,8aR)-2-(2-fluoroethyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-2,5,5,8a-tetramethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile hydrochloride;

(8aS)-2,5,5,8a-tetramethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile hydrochloride;

(4aS,8aR)-5,5,8a-trimethyl-2-(oxetan-3-yl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-2-(oxetan-3-yl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-5,5,8a-trimethyl-6-oxo-2-pyrimidin-2-yl-1,3-dihydroisoquinoline-7-carbonitrile hydrochloride;

(8aS)-5,5,8a-trimethyl-6-oxo-2-pyrimidin-2-yl-1,3-dihydroisoquinoline-7-carbonitrile hydrochloride;

(4aR,5R,8aS)-2-benzyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-benzyl-5-methyl-1,6-dioxo-8a-phenyl-3,4,4a,5-tetrahydroisoquinoline-7-carbonitrile;

(8aR)-2-(2,2-dimethylpropanoyl)-5,5,8a-trimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(8aS)-2-(2,2-dimethylpropanoyl)-5,5,8a-trimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-formyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-formyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2,2-difluoroethyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(2,2-difluoroethyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-7-cyano-N,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-2-carboxamide;

(4aR,8aS)-7-cyano-N,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-2-carboxamide;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-(2,2,2-trifluoroethyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2-(2,2,2-trifluoroethyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-pyrimidin-2-yl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2-pyrimidin-2-yl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2,2-dimethylpropanoyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(2,2-dimethylpropanoyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-2-(2-methylpropanoyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-2-(2-methylpropanoyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-propanoyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2-propanoyl-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,5S,8aR)-2-acetyl-5,8a-dimethyl-6-oxo-3,4,4a,5-tetrahydro-1H-isoquinoline-7-carbonitrile;

(4aR,5R,8aS)-2-acetyl-5,8a-dimethyl-6-oxo-3,4,4a,5-tetrahydro-1H-isoquinoline-7-carbonitrile;

(8aR)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(8aS)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3-dihydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-2-(1-methylpyrazole-4-carbonyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-2-(1-methylpyrazole-4-carbonyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2-(pyrimidine-5-carbonyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-(pyrimidine-5-carbonyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2-(pyridine-3-carbonyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2-(pyridine-3-carbonyl)-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(2-methoxyacetyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(2-methoxyacetyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-2-(oxetane-3-carbonyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-2-(oxetane-3-carbonyl)-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(cyclopropanecarbonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(cyclopropanecarbonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-butanoyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-butanoyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(cyclohexanecarbonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(cyclohexanecarbonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-benzyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-benzyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-(benzenesulfonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-(benzenesulfonyl)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-2-methylsulfonyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-5,5,8a-trimethyl-2-methylsulfonyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-benzoyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2-benzoyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aR,8aS)-2,5,5,8a-tetramethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-5,5,8a-trimethyl-6-oxo-2,3,4,4a-tetrahydro-1H-isoquinoline-7-carbonitrile hydrochloride;

(4aR,8aS)-5,5,8a-trimethyl-6-oxo-2,3,4,4a-tetrahydro-1H-isoquinoline-7-carbonitrile hydrochloride;

(4aR,8aS)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

(4aS,8aR)-2-acetyl-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisoquinoline-7-carbonitrile;

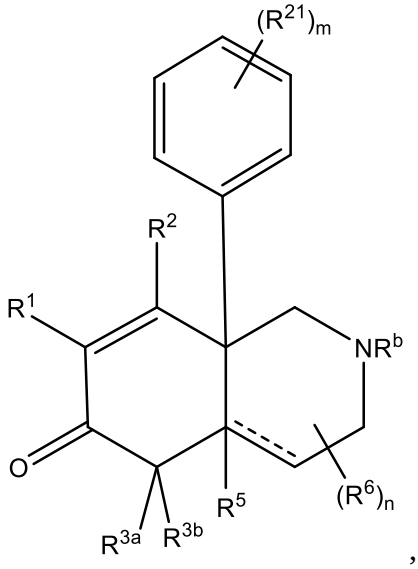
(8aS)-5,5,8a-trimethyl-6-oxo-1,3-dihydroisochromene-7-carbonitrile and

(8aS)-5,5,8a-trimethyl-6-oxo-1,3,4,4a-tetrahydroisochromene-7-carbonitrile,

and pharmaceutically acceptable salts thereof.

12. The compound of claim 1, wherein the compound is represented by:

(i) Formula XI:

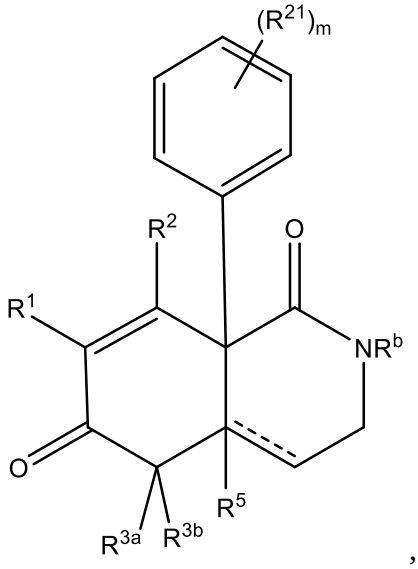


,

or a pharmaceutically acceptable salt thereof;

and wherein R^1 is optionally $-CF_3$ or -CN; or

(ii) Formula XIII:



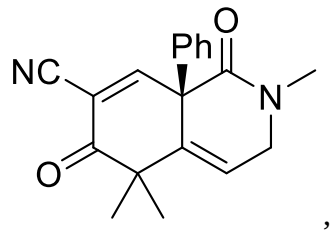
,

or a pharmaceutically acceptable salt thereof;

and wherein R^1 is optionally $-CF_3$ or -CN.

13. The compound of claim 11, wherein the compound is

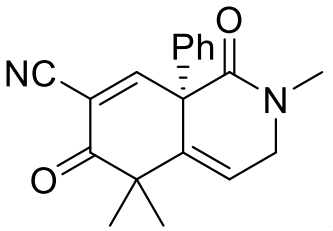
(8aR)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile represented by the following formula:



,

or a pharmaceutically acceptable salt thereof;

or (8aS)-2,5,5-trimethyl-1,6-dioxo-8a-phenyl-3H-isoquinoline-7-carbonitrile represented by the following formula:



,

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

15. Use of the compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of:

(i) a disorder, wherein the disorder is a neurodegenerative disease, inflammation/an inflammatory disease, an autoimmune disease, an ischemic fibrotic disease, a cancer, premature aging, a cardiovascular disease, a liver disease, a hemoglobinopathy or a metabolic disorder;

(ii) a hemoglobinopathy, wherein the hemoglobinopathy is sickle cell disease or thalassemia;

(iii) a neurodegenerative disorder, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, Huntington disease, amyotrophic lateral sclerosis, diffuse Lewy body disease, chorea-acanthocytosis, primary lateral sclerosis, multiple sclerosis, frontotemporal dementia, Friedreich's ataxia or epilepsy;

(iv) inflammation/an inflammatory disease, wherein the inflammation/an inflammatory disease is chronic cholecystitis, aortic valve stenosis, restenosis, a skin disease, a pulmonary diseases and a disease of the airway, inflammatory uveitis, atherosclerosis, arthritis, conjunctivitis, pancreatitis, a chronic kidney disease (CDK), an inflammatory condition associated with diabetes, an ischemia, a transplant rejection, a CD14 mediated sepsis, a non-CD14 mediated sepsis, Behcet's syndrome, ankylosing spondylitis, sarcoidosis or gout;

(v) a skin disease, wherein the skin disease is rash, contact dermatitis or atopic dermatitis;

(vi) a pulmonary diseases and a disease of the airway, wherein the pulmonary diseases and a disease of the airway is Adult Respiratory Disease Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis, an interstitial lung disease, asthma, chronic cough, allergic rhinitis, bronchiectasis or bronchitis;

(vii) an inflammatory condition associated with diabetes, wherein the an inflammatory condition associated with diabetes is a diabetic retinopathy, a diabetic cardiomyopathy or a diabetes-induced aortic damage;

(viii) an autoimmune disease, wherein the autoimmune disease is psoriasis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, systemic sclerosis or Sjogren's syndrome;

(ix) inflammatory bowel disease, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis;

(x) an ischemic fibrotic disease, wherein the ischemic fibrotic disease is stroke, acute lung injury, acute kidney injury, ischemic cardiac injury, acute liver injury or ischemic skeletal muscle injury;

(xi) a cancer, wherein the cancer is prostate cancer, bladder cancer, ovarian cancer, breast cancer (e.g., breast cancer with mutated BRCA1), head and neck cancer, chronic lymphocytic leukemia, thymus cancer, hepatocellular carcinoma, colorectal cancer, colon cancer, skin cancer, pancreatic cancer, leukemia, lung cancer, glioblastoma, cervical cancer, lymphoma, Waldenström's macroglobulinemia or multiple myeloma;

(xii) a cardiovascular disease, wherein the cardiovascular disease is pulmonary arterial hypertension, systemic hypertension, coronary artery disease, peripheral artery disease or atherosclerosis;

(xiii) a liver disease, wherein the liver disease is non-alcoholic steatohepititis (NASH), alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis;

(xiv) thalassemia, wherein the thalassemia is beta-thalassemia;

(xv) thalassemia minor, thalassemia intermedia, or thalassemia major;

(xvi) sickle cell disease, wherein the sickle cell disease is sickle retinopathy;

(xvii) a metabolic disorder, wherein the metabolic disorder is diabetes, obesity, metabolic syndrome or hypertension; or

(xviii) diabetes, wherein the diabetes is type 1 diabetes, type 2 diabetes or gestational diabetes.