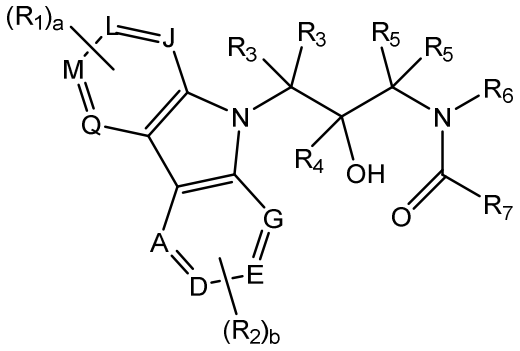
CLAIMS

1. A compound of formula I



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

each of A, D, E, G, J, L, M, and Q is independently nitrogen or carbon;

each of R_1 and R_2, when A, D, E, G, J, L, M, or Q is carbon, is independently selected from hydrogen, halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-O-(C=O)-R_8$, $-NR_8(C=O)-R_{10}$, $-(C=O)-NR_8R_9$, $-NR_8R_9$, $-NR_8OR_9$, $-S(O)_cNR_8R_9$, $-S(O)_d(C_1$-$C_8)$alkyl, $-O-SO_2-R_8$, $NR_8-S(O)_c$, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$aryl, $-(CR_8R_9)_eO(CR_8R_9)_f$(4-10)-membered heterocyclyl, $-(CR_8R_9)_fS(O)_d(CR_8R_9)_e(C_6$-$C_{10})$aryl, and $–(CR_8R_9)_fS(O)_d(CR_8R_9)_e$(4-10)-membered heterocyclyl;

each of R_3 and R_5 is independently selected from hydrogen, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-S(O)_cNR_8R_9$, $-S(O)_d(C_1$-$C_8)$alkyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$aryl, $-(CR_8R_9)_eO(CR_8R_9)_f$(4-10)-membered heterocyclyl, $-(CR_8R_9)_fS(O)_d(CR_8R_9)_e(C_6$-$C_{10})$aryl, and $–(CR_8R_9)_fS(O)_d(CR_8R_9)_e$(4-10)-membered heterocyclyl;

wherein each of the R_3 groups are optionally linked to each other as a 4-12 membered mono- or bicyclic ring;

wherein each of the R_5 groups are optionally linked to each other as a 4-12 membered mono- or bicyclic ring;

R_4 is hydrogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-(C=O)\text{-}R_8$, $-(C=O)\text{-}O\text{-}R_8$, $-(C=O)\text{-}NR_8R_9$, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6\text{-}C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e(C_6\text{-}C_{10})$aryl, $-(CR_8R_9)_f(C=O)(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6\text{-}C_{10})$aryl, $-(CR_8R_9)_eO(CR_8R_9)_f$(4-10)-membered heterocyclyl, $-CR_8R_9)_fS(O)_d(CR_8R_9)_e(C_6\text{-}C_{10})$aryl, and $-(CR_8R_9)_fS(O)_d(CR_8R_9)_e$(4-10)-membered heterocyclyl;

wherein R_6 and R_7 are linked to each other as a 4-12 membered mono- or bicyclic ring optionally substituted with one or more halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_{10})$cycloalkyl, or $(C_6\text{-}C_{10})$aryl;

each of R_8, R_9 and R_{10} are independently selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $-(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, $-(CR_{11}R_{12})_g(C_6\text{-}C_{10})$aryl, and $-(CR_{11}R_{12})_g$(4-10)-membered heterocyclyl;

any carbon atoms of the $(C_1\text{-}C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6\text{-}C_{10})$aryl and the (4-10)-membered heterocyclyl of the foregoing R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, and R_{16} are independently optionally substituted with 1 to 3 R_{14} substituents each independently selected from halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxyl, $-O\text{-}R_{15}$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-(C=O)\text{-}R_{11,}$ $-(C=O)\text{-}R_{15}$, $-(C=O)\text{-}O\text{-}R_{11,}$ $-(C=O)\text{-}O\text{-}R_{15}$, $-O\text{-}(C=O)\text{-}R_{11}$, $-O\text{-}(C=O)\text{-}R_{15}$, -NR11(C=O)-$R_{13}$, $-(C=O)\text{-}NR_{11}R_{12}$, $-(C=O)\text{-}NR_{11}R_{15}$, $-NR_{11}R_{12}$, $-NR_{11}R_{15}$, $-NR_{11}OR_{12}$, $-NR_{11}OR_{15}$, $-S(O)_cNR_{11}R_{12}$, $-S(O)_cNR_{11}R_{15}$, $-S(O)_d(C_1\text{-}C_6)$alkyl, $-S(O)_dR_{15}$, $-O\text{-}SO_2\text{-}R_{11}$, $-O\text{-}SO_2\text{-}R_{15}$, $-NR_{11}\text{-}S(O)_c$, $-NR_{15}\text{-}S(O)_c$, $-(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, $-(CR_{11}R_{12})_e(C_6\text{-}C_{10})$aryl, $-(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl, $-(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e(C_6\text{-}C_{10})$aryl, $-(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl, $-(CR_{11}R_{12})_eO(CR_{11}R_{12})_f(C_6\text{-}C_{10})$aryl,

-$(CR_{11}R_{12})_eO(CR_{11}R_{12})_f$(4-10)-membered heterocyclyl, -$(CR_{11}R_{12})_fS(O)_d(CR_{11}R_{12})_e(C_6$-$C_{10})$aryl, and -$(CR_{11}R_{12})_fS(O)_d(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl;

any carbon atoms of the $(C_1$-$C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6$-$C_{10})$aryl and the (4-10)-membered heterocyclyl of the foregoing R_{14} are independently optionally substituted with 1 to 3 R_{16} substituents each independently selected from halo, cyano, nitro, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, azido, $(CH_2)_eOH$, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(C=O)$-R_{11}, -$(C=O)$-R_{15}, -$(C=O)$-O-R_{11}, -$(C=O)$-O-R_{15}, -O-$(C=O)$-R_{11}, -O-$(C=O)$-R_{15}, -$NR_{11}(C=O)$-R_{13}, -$(C=O)$-$NR_{11}R_{12}$, -$NR_{11}R_{12}$, and –$NR_{11}R_{15}$;

any nitrogen atoms of the (4-10)-membered heterocyclyl of the foregoing R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{14}, and R_{15} are independently optionally substituted with $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(C=O)$-R_{11}, -$(C=O)$-O-R_{11}, -$(C=O)$-$NR_{11}R_{12}$, -$(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, -$(CR_{11}R_{12})_e(C_6$-$C_{10})$aryl, -$(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl, -$(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e(C_6$-$C_{10})$aryl, or -$(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl;

each R_{11}, R_{12}, and R_{13} are independently hydrogen or $(C_1$-$C_6)$alkyl;

R_{15} is –$(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, -$(CR_{11}R_{12})_e(C_6$-$C_{10})$aryl, or –$(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl;

a and b are each independently 1, 2, 3, or 4;

c is 1 or 2;

d is 0, 1, or 2; and

e, f, and g are each independently 0, 1, 2, 3, 4, or 5.

2. The compound according to claim 1, wherein each of A, D, E, G, J, L, M, and Q are carbon; each of R_1 and R_2 is independently selected from hydrogen or halo; R_4 is hydrogen or $(C_1$-$C_6)$alkyl, R_3 and R_5 are hydrogen; R_6 and R_7 are linked to each other as a 4-12 membered mono- or bicyclic amide ring.

3. The compound according to claim 1, wherein each of A, D, E, G, J, L, M, and Q are carbon; each of R_1 and R_2 is independently selected from hydrogen or halo; R_4 is hydrogen or (C_1-C_6)alkyl, R_3 and R_5 are hydrogen; R_6 and R_7 are linked to each other as a 4-12 membered mono- or bicyclic urea ring.

4. The compound according to claim 1, wherein the compound is the single enantiomer bearing an (*R*)-configuration at C-3, each of A, D, E, G, J, L, M, and Q are carbon; each of R_1 and R_2 is independently selected from hydrogen or halo; R_4 is hydrogen or (C_1-C_6)alkyl, R_3 and R_5 are hydrogen; R_6 and R_7 are linked to each other as a 4-12 membered mono- or bicyclic amide ring.

5. The compound according to claim 1, wherein the compound is the single enantiomer bearing an (*R*)-configuration at C-3, each of A, D, E, G, J, L, M, and Q are carbon; each of R_1 and R_2 is independently selected from hydrogen or halo; R_4 is hydrogen or (C_1-C_6)alkyl, R_3 and R_5 are hydrogen; R_6 and R_7 are linked to each other as a 4-12 membered mono- or bicyclic urea ring.

6. The compound according to claim 1, wherein the compound is selected from the group consisting of:

1-(3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-3-fluoropyrrolidin-2-one;

2-(3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-3-one;

1-(3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one;

(*1R,4S*)-2-((*R*)-3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-3-one;

(*R*)-1-(3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one;

(*R*)-1-((*R*)-3-(3,6-difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-3-fluoropyrrolidin-2-one;

(*S*)-1-((*S*)-3-(9H-carbazol-9-yl)-2-hydroxy-2-methylpropyl)-3-fluoropyrrolidin-2-one; and

(*R*)-1-((*R*)-3-(9H-carbazol-9-yl)-2-hydroxypropyl)-4-methylimidazolidin-2-one;

or a pharmaceutically acceptable salt or hydrate thereof.

7. The use of the compound according to claim 1 in the manufacture of a medicament for the modulation of Cry1 or Cry2.

8. The use according to claim 7, wherein said modulation comprises any one of the following:

(i) binding to Cry1 or Cry2;

(ii) inhibiting modification of Cry1 or Cry2;

(iii) altering Cry1 or Cry2 localization;

(iv) increasing or decreasing Cry1 or Cry2 stabilization;

(v) increasing or decreasing the binding between Cry1 or Cry2 to a target;

(vi) increasing or decreasing Cry1 or Cry2 activity; and

(vii) increasing or decreasing activity of a Cry1 or Cry2 target.

9. The use according to claim 8, wherein said target is Per1, Per2, glucocorticoid receptor (GR), CLOCK, BMAL1, or a CLOCK-BMAL1 promoter sequence.

10. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

11. The pharmaceutical composition according to claim 10, further comprising one or more additional therapeutic agents.

12. The pharmaceutical composition according to claim 11, wherein said one or more additional therapeutic agents is selected from the group consisting of DPP-IV inhibitors, SGLT2 inhibitors, metformin, sulfonylureas, Signifor®, ketoconazole, metyrapone, mitotane, etomidate, Korlym®, epidermal growth factor receptor inhibitors, the aldosterone synthase/11β-hydroxylase inhibitor LCI699, and levoketoconazole (COR-003).

13. Use of the pharmaceutical composition according to claim 10 in the manufacture of a medicament for the treatment of a Cry-mediated disease or.

14. Use of the pharmaceutical composition according to claim 10 in the manufacture of a medicament for alleviating a symptom of a Cry-mediated disease or disorder.

15. The use according to claims 13 or 14, wherein the Cry-mediated disease or disorder is selected from the group consisting of diabetes, diabetes, diabetic complications such as diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract formation, glaucoma, diabetic angiopathy, atherosclerosis; nonalcoholic steatohepatitis (NASH); non-alcoholic fatty liver disease (NAFLD); asthma; chronic obstructive pulmonary disease (COPD); metabolic syndrome; insulin resistance syndrome; obesity; glaucoma; Cushing's syndrome; psychotic depression; Alzheimer's disease; neuropathic pain; drug abuse; osteoporosis; cancer; macular degeneration; and myopathy.

16. The use according to claims 13 or 14, further comprising administering to the subject one or more additional therapeutic agents.

17. The use according to claim 16, wherein said one or more additional therapeutic agents is selected from the group consisting of DPP-IV inhibitors, SGLT2 inhibitors, metformin, sulfonylureas, Signifor®, ketoconazole, metyrapone, mitotane, etomidate, Korlym®, epidermal growth factor receptor inhibitors, the aldosterone synthase/11β-hydroxylase inhibitor LCI699, and levoketoconazole (COR-003).

18. The compound according to claim 1, wherein A, D, E, G, J, L, M, and Q are carbon.

19. The compound according to claim 1, wherein R_1 and R_2 are hydrogen.

20. The compound according to claim 1, wherein R_1 and R_2 are fluorine, and a and b are 1.

21. The compound according to claim 1, wherein R_3 and R_5 are hydrogen.

22. The compound according to claim 1, wherein R_3, R_4, and R_5 are hydrogen.

23. The compound according to claim 1, wherein R_6 and R_7 are linked to form an optionally substituted monocyclic ring, optionally substituted fused bicyclic ring, optionally substituted bridged bicyclic ring, optionally substituted spiro bicyclic ring, optionally substituted

pyrrolidinone ring, optionally substituted imidazolidinone ring, optionally substituted piperidinone ring, optionally substituted pyrimidinone ring,

24. The compound according to claim 23, wherein the ring formed by R_6 and R_7 is substituted with one or more fluorine, methyl, ethyl, isopropyl, methoxy, C_{3-6} cycloalkyl, or phenyl.

25. The compound according to claim 1, wherein R_6 and R_7 are linked to each other as a 5-membered mono- or bicyclic ring, 7-membered mono- or bicyclic ring, 10-membered mono- or bicyclic ring, piperidinone ring, or morpholinone ring, optionally substituted with one or more halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl, or (C_6-C_{10})aryl.

26. The compound according to claim 1, wherein R_6 and R_7 are linked to each other as a saturated 2-pyrimidinone ring, which is unsubstituted or substituted with one or more halo, (C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl, or (C_6-C_{10})aryl.