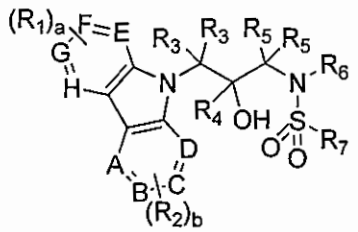
## CLAIMS

What is claimed is:

1. A compound of formula I



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

each of A, B, C, D, E, F, G, and H is independently N or C;

each of $R_1$ and $R_2$, when A, B, C, D, E, F, G, or H is C, is independently selected from H, 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 H, 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 H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(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;

$R_6$ is H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(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;

$R_5$ and $R_6$ are optionally linked to each other as a 4-12 membered mono- or bicyclic ring;

$R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-NR_8(C=O)-R_{10}$, $-(C=O)-NR_8R_9$, $-NR_8R_9$, $-NR_8OR_9$, $-NR_8-S(O)_c$, $-(CR_8R_9)_d$(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;

$R_6$ and $R_7$ can be linked to each other as a 4-12 membered mono- or bicyclic ring;

each of $R_8$, $R_9$ and $R_{10}$ are independently selected from H, $(C_1-C_6)$alkyl, $-(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, $-(CR_{11}R_{12})_g(C_6-C_{10})$aryl, and $-(CR_{11}R_{12})_g$(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 $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, 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, $-O-R_{15}$, $(C_1$-$C_6)$alkoxy, $-(CR_8R_9)_e(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R_{11}$, $-(C=O)-R_{15}$, $-(C=O)-O-R_{11}$, $-(C=O)-O-R_{15}$, $-O-(C=O)-R_{11}$, $-O-(C=O)-R_{15}$, $-NR11(C=O)-R_{13}$, $-(C=O)-NR_{11}R_{12}$, $-(C=O)-NR_{11}R_{15}$, $-NR_{11}R_{12}$, $-NR_{11}R_{15}$, $-NR_{11}OR_{12}$, $-NR_{11}OR_{15}$, $-S(O)_cNR_{11}R_{12}$, $-S(O)_cNR_{11}R_{15}$, $-S(O)_d(C_1$-$C_6)$alkyl, $-S(O)_dR_{15}$, $-O-SO_2-R_{11}$, $-O-SO_2-R_{15}$, $-NR_{11}-S(O)_c$, $-NR_{15}-S(O)_c$, $-(CR_{11}R_{12})_e$(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, $-(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl, $-(CR_{11}R_{12})_eO(CR_{11}R_{12})_f(C_6$-$C_{10})$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 H 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, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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; $R_7$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

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

4. The compound according to claim 1, wherein each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl; $R_3$ and one $R_5$ are H; one $R_5$ and $R_6$ are linked to each other as a 4-12 membered mono- or bicyclic ring; $R_7$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

5. The compound according to claim 1, wherein the compound is the single enantiomer bearing an (*S*)-configuration at C-3, each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$

is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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; $R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

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

7. A compound selected from the group consisting of:

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide;

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide;

2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide;

N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

8. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 7 which is N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

10. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

11. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

12. The compound according to claim 7 which is 2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

13. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide; or a pharmaceutically acceptable salt or hydrate thereof.

14. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

15. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

16. The compound according to claim 7 which is N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

17. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

18. The compound according to claim 1, wherein said compound modulates Cry1 or Cry2.

19. The compound according to claim 18, 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.

20. The compound according to claim 19, wherein said target is Per1, Per2, glucocorticoid receptor (GR), CLOCK, BMAL1, or a CLOCK-BMAL1 promoter sequence.

21. 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.

22. The pharmaceutical composition according to claim 21, further comprising one or more additional therapeutic agents.

23. A method of treating a Cry-mediated disease or disorder in a subject, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to claim 21.

24. A method of alleviating a symptom of a Cry-mediated disease or disorder in a subject, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to claim 21.

25. The method according to claim 23 or 24 wherein the Cry-mediated disease or disorder is diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, and

glaucoma. psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.

26. The method according to claim 23 or 24, further comprising administering to the subject one or more additional therapeutic agents.

27. A method of monitoring progression or prognosis of a Cry-mediated disease or disorder in a subject, comprising:

measuring an effective amount of one or more cryptochromes in a first sample from the subject at a first period of time;

measuring an affective amount of one or more cryptochromes in a second sample from the subject at a second period of time; and

comparing the amount of the one or more cryptochromes detected in the first sample to the amount of the one or more cryptochromes detected in the second sample, or to a reference value.

28. The method according to claim 27, wherein the monitoring comprises evaluating changes in the risk of developing the Cry-mediated disease or disorder in the subject.

29. The method according to claim 27, wherein the subject comprises one who has been previously treated for the Cry-mediated disease or disorder, one who has not been previously treated for the Cry-mediated disease or disorder, or one who has not been previously diagnosed with the Cry-mediated disease or disorder.

30. The method according to claim 27, wherein the sample is whole blood, serum, plasma, blood cells, endothelial cells, tissue biopsies, lymphatic fluid, ascites fluid, interstitial fluid, bone marrow, cerebrospinal fluid (CSF), seminal fluid, saliva, mucous, sputum, sweat, or urine.

31. The method according to claim 27, wherein the first sample is taken from the subject prior to being treated for the Cry-mediated disease or disorder.

32. The method according to claim 27, wherein the second sample is taken from the subject after being treated for the Cry-mediated disease or disorder.

33. The method according to claim 27, wherein the subject is treated with the pharmaceutical composition of claim 21.

34. The method according to claim 27, wherein the monitoring further comprises selecting a treatment for the subject and/or monitoring the effectiveness of a treatment for the Cry-mediated disease or disorder.

35. The method according to claim 34, wherein the treatment for the Cry-mediated disease or disorder comprises surgical intervention, administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, surgical intervention following or preceded by administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, or taking no further action.

36. The method according to claim 27, wherein the reference value comprises an index value, a value derived from one or more Cry-mediated disease or disorder risk prediction algorithms, a value derived from a subject not having a Cry-mediated disease or disorder, or a value derived from a subject diagnosed with a Cry-mediated disease or disorder.

37. The method according to claim 27, wherein the measuring comprises detecting the presence or absence of the one or more cryptochromes, quantifying the amount of the one or more cryptochromes, qualifying the type of the one or more cryptochromes, and assessing the ability of one or more cryptochromes to bind to a target.

38. The method according to claim 37, wherein the target is Per1, Per2, glucocorticoid receptor (GR) or a CLOCK-BMAL1 promoter sequence.

39. The method according to claim 27, wherein the Cry-mediated disease or disorder is selected from the group consisting of diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, and glaucoma. psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.

**Please enter the following amendments:**

**In the Claims:**

On page 196, line 20, claim 1 has been amended to delete reference to "$(CR_8R_9)_e(C_6$-$C_{10})$ aryl" as a species of the $R_7$ substituent.

On page 198, line 5, claim 1 has been amended to recite "and wherein when $R_7$ is $CH_3$,

$R_6$ is H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(4-10)-membered non-aromatic 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, $-(CR_8R_9)_fS(O)_g(CR_8R_9)_e(C_6$-$C_{10})$aryl, and $-(CR_8R_9)_fS(O)_d(CR_8R_9)_e$(4-10)-membered heterocyclyl".

On page 198, line 11, claim 2 has been amended to delete reference to "$(CR_8R_9)_e(C_6$-$C_{10})$ aryl" as a species of the $R_7$ substituent.

On page 198, line 23, claim 4 has been amended to delete reference to "$(CR_8R_9)_e(C_6$-$C_{10})$ aryl" as a species of the $R_7$ substituent.

On page 199, line 7, claim 5 has been amended to delete reference to "$(CR_8R_9)_e(C_6$-$C_{10})$ aryl" as a species of the $R_7$ substituent.

On page 199, line 14, claim 7 is amended to properly depend from claim 1.

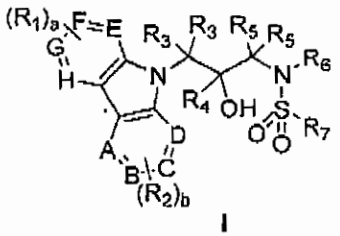


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## CLAIMS

What is claimed is:

1. A compound of formula I



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

each of A, B, C, D, E, F, G, and H is independently N or C;

each of $R_1$ and $R_2$, when A, B, C, D, E, F, G, or H is C, is independently selected from H, 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 H, 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;



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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 H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(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;

$R_6$ is H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(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;

$R_5$ and $R_6$ are optionally linked to each other as a 4-12 membered mono- or bicyclic ring;

$R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-NR_8(C=O)-R_{10}$, $-(C=O)-NR_8R_9$, $-NR_8R_9$, $-NR_8OR_9$, $-NR_8-S(O)_c$, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(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;

$R_6$ and $R_7$ can be linked to each other as a 4-12 membered mono- or bicyclic ring;

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



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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 $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, 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, $-O-R_{15}$, $(C_1$-$C_6)$alkoxy, $-(CR_8R_9)_e(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R_{11}$, $-(C=O)-R_{15}$, $-(C=O)-O-R_{11}$, $-(C=O)-O-R_{15}$, $-O-(C=O)-R_{11}$, $-O-(C=O)-R_{15}$, $-NR11(C=O)-R_{13}$, $-(C=O)-NR_{11}R_{12}$, $-(C=O)-NR_{11}R_{15}$, $-NR_{11}R_{12}$, $-NR_{11}R_{15}$, $-NR_{11}OR_{12}$, $-NR_{11}OR_{15}$, $-S(O)_cNR_{11}R_{12}$, $-S(O)_cNR_{11}R_{15}$, $-S(O)_d(C_1$-$C_6)$alkyl, $-S(O)_dR_{15}$, $-O-SO_2-R_{11}$, $-O-SO_2-R_{15}$, $-NR_{11}-S(O)_c$, $-NR_{15}-S(O)_c$, $-(CR_{11}R_{12})_e$(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, $-(CR_{11}R_{12})_f(C=O)(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl, $-(CR_{11}R_{12})_eO(CR_{11}R_{12})_f(C_6$-$C_{10})$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 H 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;



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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;

and wherein when $R_7$ is $CH_3$,

$R_6$ is H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(C=O)-R_8$, $-(C=O)-O-R_8$, $-(C=O)-NR_8R_9$, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(4-10)-membered non-aromatic 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.

2. The compound according to claim 1, wherein each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1-C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6-C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6-C_{10})$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; $R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(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.

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

4. The compound according to claim 1, wherein each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1-C_6)$alkyl; $R_3$ and one



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$R_5$ are H, one $R_5$ and $R_6$ are linked to each other as a 4-12 membered mono- or bicyclic ring; $R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(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.

5. The compound according to claim 1, wherein the compound is the single enantiomer bearing an (*S*)-configuration at C-3, each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1-C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6-C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6-C_{10})$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; $R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1-C_6)$alkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e$(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.

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

7. The compound of claim 1, wherein said compound is selected from the group consisting of:

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide;

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide;



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2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide;

N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

8. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 7 which is N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

10. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

11. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

12. The compound according to claim 7 which is 2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

13. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide; or a pharmaceutically acceptable salt or hydrate thereof.



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14. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

15. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

16. The compound according to claim 7 which is N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

17. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

18. The compound according to claim 1, wherein said compound modulates Cry1 or Cry2.

19. The compound according to claim 18, 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.

20. The compound according to claim 19, wherein said target is Per1, Per2, glucocorticoid receptor (GR), CLOCK, BMAL1, or a CLOCK-BMAL1 promoter sequence.

21. 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.



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22. The pharmaceutical composition according to claim 21, further comprising one or more additional therapeutic agents.

23. A method of treating a Cry-mediated disease or disorder in a subject, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to claim 21.

24. A method of alleviating a symptom of a Cry-mediated disease or disorder in a subject, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to claim 21.

25. The method according to claim 23 or 24 wherein the Cry-mediated disease or disorder is diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, and glaucoma. psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.

26. The method according to claim 23 or 24, further comprising administering to the subject one or more additional therapeutic agents.

27. A method of monitoring progression or prognosis of a Cry-mediated disease or disorder in a subject, comprising:

measuring an effective amount of one or more cryptochromes in a first sample from the subject at a first period of time;

measuring an affective amount of one or more cryptochromes in a second sample from the subject at a second period of time; and

comparing the amount of the one or more cryptochromes detected in the first sample to the amount of the one or more cryptochromes detected in the second sample, or to a reference value.

28. The method according to claim 27, wherein the monitoring comprises evaluating changes in the risk of developing the Cry-mediated disease or disorder in the subject.



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29. The method according to claim 27, wherein the subject comprises one who has been previously treated for the Cry-mediated disease or disorder, one who has not been previously treated for the Cry-mediated disease or disorder, or one who has not been previously diagnosed with the Cry-mediated disease or disorder.

30. The method according to claim 27, wherein the sample is whole blood, serum, plasma, blood cells, endothelial cells, tissue biopsies, lymphatic fluid, ascites fluid, interstitial fluid, bone marrow, cerebrospinal fluid (CSF), seminal fluid, saliva, mucous, sputum, sweat, or urine.

31. The method according to claim 27, wherein the first sample is taken from the subject prior to being treated for the Cry-mediated disease or disorder.

32. The method according to claim 27, wherein the second sample is taken from the subject after being treated for the Cry-mediated disease or disorder.

33. The method according to claim 27, wherein the subject is treated with the pharmaceutical composition of claim 21.

34. The method according to claim 27, wherein the monitoring further comprises selecting a treatment for the subject and/or monitoring the effectiveness of a treatment for the Cry-mediated disease or disorder.

35. The method according to claim 34, wherein the treatment for the Cry-mediated disease or disorder comprises surgical intervention, administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, surgical intervention following or preceded by administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, or taking no further action.

36. The method according to claim 27, wherein the reference value comprises an index value, a value derived from one or more Cry-mediated disease or disorder risk prediction algorithms, a value derived from a subject not having a Cry-mediated disease or disorder, or a value derived from a subject diagnosed with a Cry-mediated disease or disorder.



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37. The method according to claim 27, wherein the measuring comprises detecting the presence or absence of the one or more cryptochromes, quantifying the amount of the one or more cryptochromes, qualifying the type of the one or more cryptochromes, and assessing the ability of one or more cryptochromes to bind to a target.

38. The method according to claim 37, wherein the target is Per1, Per2, glucocorticoid receptor (GR) or a CLOCK-BMAL1 promoter sequence.

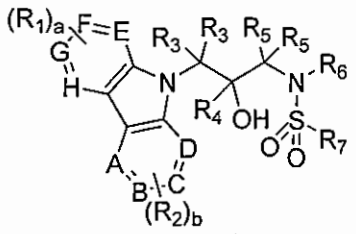
39. The method according to claim 27, wherein the Cry-mediated disease or disorder is selected from the group consisting of diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, and glaucoma. psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.



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What is claimed is:

1. A compound of formula I



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

each of A, B, C, D, E, F, G, and H is independently N or C;

each of $R_1$ and $R_2$, when A, B, C, D, E, F, G, or H is C, is independently selected from H, 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, $-(CR_8R_9)_fS(O)_d(CR_8R_9)_c(C_6-C_{10})$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 H, 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 H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1\text{-}C_6)$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;

$R_6$ is H, $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1\text{-}C_6)$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;

$R_5$ and $R_6$ are optionally linked to each other as a 4-12 membered mono- or bicyclic ring;

$R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-(C=O)\text{-}R_8$, $-(C=O)\text{-}O\text{-}R_8$, $-NR_8(C=O)\text{-}R_{10}$, $-(C=O)\text{-}NR_8R_9$, $-NR_8R_9$, $-NR_8OR_9$, $-NR_8\text{-}S(O)_c$, $-(CR_8R_9)_d$(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;

$R_6$ and $R_7$ can be linked to each other as a 4-12 membered mono- or bicyclic ring;

each of $R_8$, $R_9$ and $R_{10}$ are independently selected from H, $(C_1\text{-}C_6)$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, $-O-R_{15}$, $(C_1\text{-}C_6)$alkoxy, $-(CR_8R_9)_e(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-(C=O)-R_{11}$, $-(C=O)-R_{15}$, $-(C=O)-O-R_{11}$, $-(C=O)-O-R_{15}$, $-O-(C=O)-R_{11}$, $-O-(C=O)-R_{15}$, $-NR11(C=O)-R_{13}$, $-(C=O)-NR_{11}R_{12}$, $-(C=O)-NR_{11}R_{15}$, $-NR_{11}R_{12}$, $-NR_{11}R_{15}$, $-NR_{11}OR_{12}$, $-NR_{11}OR_{15}$, $-S(O)_cNR_{11}R_{12}$, $-S(O)_cNR_{11}R_{15}$, $-S(O)_d(C_1\text{-}C_6)$alkyl, $-S(O)_dR_{15}$, $-O-SO_2-R_{11}$, $-O-SO_2-R_{15}$, $-NR_{11}-S(O)_c$, $-NR_{15}-S(O)_c$, $-(CR_{11}R_{12})_e$(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, $-(CR_{11}R_{12})_fS(O)_d(CR_{11}R_{12})_e(C_6\text{-}C_{10})$aryl, and $-(CR_{11}R_{12})_fS(O)_d(CR_{11}R_{12})_e$(4-10)-membered heterocyclyl;

any carbon atoms of the $(C_1\text{-}C_6)$alkyl, the (3-10)-membered cycloalkyl, the $(C_6\text{-}C_{10})$aryl and the (4-10)-membered heterocyclyl of the foregoing $R_{14}$ 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, $(CH_2)_eOH$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$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 $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$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, $-(CR_{11}R_{12})_e(C_6\text{-}C_{10})$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, 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 H or $(C_1\text{-}C_6)$alkyl;

$R_{15}$ is $-(CR_{11}R_{12})_e$(3-10)-membered cycloalkyl, $-(CR_{11}R_{12})_e(C_6\text{-}C_{10})$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, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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; $R_7$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

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

4. The compound according to claim 1, wherein each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$ is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl; $R_3$ and one $R_5$ are H; one $R_5$ and $R_6$ are linked to each other as a 4-12 membered mono- or bicyclic ring; $R_7$ is -$CF_3$, -$CHF_2$, -$CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR_8R_9)_d$(3-10)-membered cycloalkyl, -$(CR_8R_9)_e(C_6$-$C_{10})$aryl, -$(CR_8R_9)_e$(4-10)-membered heterocyclyl, -$(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

5. The compound according to claim 1, wherein the compound is the single enantiomer bearing an (*S*)-configuration at C-3, each of A, B, C, D, E, F, G, and H are C; each of $R_1$ and $R_2$

is independently selected from H or halo; $R_4$ is H or $(C_1$-$C_6)$alkyl, $R_3$ and $R_5$ are H; $R_6$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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; $R_7$ is $-CF_3$, $-CHF_2$, $-CH_2F$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR_8R_9)_d$(3-10)-membered cycloalkyl, $-(CR_8R_9)_e(C_6$-$C_{10})$aryl, $-(CR_8R_9)_e$(4-10)-membered heterocyclyl, $-(CR_8R_9)_eO(CR_8R_9)_f(C_6$-$C_{10})$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.

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

7. A compound selected from the group consisting of:

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide;

(S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide;

2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide;

N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide;

N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide;

2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

8. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 7 which is N-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

10. The compound according to claim 7 which is (S)-N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

11. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-5-fluoro-isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

12. The compound according to claim 7 which is 2-(3-(3,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

13. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-N-(1-methylcyclopentyl)methanesulfonamide; or a pharmaceutically acceptable salt or hydrate thereof.

14. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)isothiazolidine-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

15. The compound according to claim 7 which is N-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

16. The compound according to claim 7 which is N-(3-(2,6-Difluoro-9H-carbazol-9-yl)-2-hydroxypropyl)-1,2-thiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

17. The compound according to claim 7 which is 2-(3-(9H-Carbazol-9-yl)-2-hydroxypropyl)-1,2,6-thiadiazinane-1,1-dioxide; or a pharmaceutically acceptable salt or hydrate thereof.

18. The compound according to claim 1, wherein said compound modulates Cry1 or Cry2.

19. The compound according to claim 18, 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.

20. The compound according to claim 19, wherein said target is Per1, Per2, glucocorticoid receptor (GR), CLOCK, BMAL1, or a CLOCK-BMAL1 promoter sequence.

21. 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.

22. The pharmaceutical composition according to claim 21, further comprising one or more additional therapeutic agents.

23. A pharmaceutical composition according to claim 21 for use in the treatment of a Cry-mediated disease or disorder.

24. A pharmaceutical composition according to claim 21 for use in alleviating a symptom of a Cry-mediated disease or disorder.

25. The pharmaceutical composition according to claim 23 or 24 wherein the Cry-mediated disease or disorder is diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, glaucoma, psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.

26. The pharmaceutical composition according to claim 23 or 24, further comprising the use of one or more additional therapeutic agents.

27. A method of monitoring progression or prognosis of a Cry-mediated disease or disorder in a subject, comprising:

measuring an effective amount of one or more cryptochromes in a first sample from the subject at a first period of time;

measuring an affective amount of one or more cryptochromes in a second sample from the subject at a second period of time; and

comparing the amount of the one or more cryptochromes detected in the first sample to the amount of the one or more cryptochromes detected in the second sample, or to a reference value.

28. The method according to claim 27, wherein the monitoring comprises evaluating changes in the risk of developing the Cry-mediated disease or disorder in the subject.

29. The method according to claim 27, wherein the subject comprises one who has been previously treated for the Cry-mediated disease or disorder, one who has not been previously treated for the Cry-mediated disease or disorder, or one who has not been previously diagnosed with the Cry-mediated disease or disorder.

30. The method according to claim 27, wherein the sample is whole blood, serum, plasma, blood cells, endothelial cells, tissue biopsies, lymphatic fluid, ascites fluid, interstitial fluid, bone marrow, cerebrospinal fluid (CSF), seminal fluid, saliva, mucous, sputum, sweat, or urine.

31. The method according to claim 27, wherein the first sample is taken from the subject prior to being treated for the Cry-mediated disease or disorder.

32. The method according to claim 27, wherein the second sample is taken from the subject after being treated for the Cry-mediated disease or disorder.

33. The method according to claim 27, wherein the subject is treated with the pharmaceutical composition of claim 21.

34. The method according to claim 27, wherein the monitoring further comprises selecting a treatment for the subject and/or monitoring the effectiveness of a treatment for the Cry-mediated disease or disorder.

35. The method according to claim 34, wherein the treatment for the Cry-mediated disease or disorder comprises surgical intervention, administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, surgical intervention following or preceded by administration of the pharmaceutical composition of claim 21 alone or in combination with one or more additional therapeutic agents, or taking no further action.

36. The method according to claim 27, wherein the reference value comprises an index value, a value derived from one or more Cry-mediated disease or disorder risk prediction algorithms, a value derived from a subject not having a Cry-mediated disease or disorder, or a value derived from a subject diagnosed with a Cry-mediated disease or disorder.

37. The method according to claim 27, wherein the measuring comprises detecting the presence or absence of the one or more cryptochromes, quantifying the amount of the one or more cryptochromes, qualifying the type of the one or more cryptochromes, and assessing the ability of one or more cryptochromes to bind to a target.

38. The method according to claim 37, wherein the target is Per1, Per2, glucocorticoid receptor (GR) or a CLOCK-BMAL1 promoter sequence.

39. The method according to claim 27, wherein the Cry-mediated disease or disorder is selected from the group consisting of diabetes, obesity, metabolic syndrome, insulin resistance syndrome, Cushing's syndrome, glaucoma, psychotic depression, Alzheimer's disease, neuropathic pain, drug abuse, osteoporosis, cancer, macular degeneration, and myopathy.