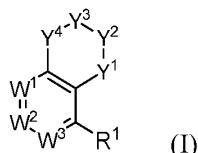


WHAT IS CLAIMED IS:

1 1. A compound represented by Formula (I)



2 or a pharmaceutically acceptable salt thereof, wherein:

3 Y¹, Y², Y³ and Y⁴ are each independently selected from the group consisting of CR²R³, NR⁴,

4 CR⁶R⁷, NR⁷, O, SO₂, and a bond; and one of Y¹, Y², Y³ and Y⁴ is CR⁶R⁷ or NR⁷; and no

5 more than one of Y¹, Y², Y³ and Y⁴ is a bond;

6 W¹, W², and W³ are each independently selected from the group consisting of CR⁵ and N;

7 R¹ is selected from the group consisting of H, halogen, hydroxy, CN, NO₂, -NR^aR^b, C₁₋₄ alkyl,

8 C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈

9 cycloalkyl, -S(O)₂R^a, -C(O)NR^aR^b, -S(O)(=NH)R^a, and -S(O)₂NR^aR^b;

10 each R² and R³ are each independently selected from the group consisting of H, halogen, CN,

11 NO₂, OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄

12 alkoxyC₁₋₄alkyl, C₃₋₈ cycloalkyl, -S(O)₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b,

13 -S(O)(=NH)R^a, and -NR^aR^b;

14 each R⁴ is independently selected from H, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, and -C(O)R^a,

15 each R⁵ is independently selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl,

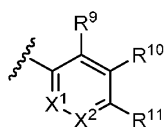
16 C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈

17 cycloalkyl, -S(O)₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, -S(O)(=NH)R^a,

18 and -NR^aR^b;

19 R⁶ is selected from the group consisting of H, C₁₋₄ alkyl, OH, F and CN;

20 R⁷ is a group having the formula:



21 wherein:

22 X¹ is N or CR^{8a};

23 X² is N or CR^{8b};

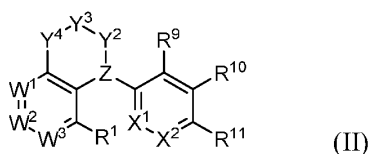
26 R^{8a} and R^{8b} are independently selected from the group consisting of H, halogen, CN, NO₂,
 27 C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄
 28 alkoxyC₁₋₄alkyl, C₃₋₆ cycloalkyl, -C(O)NR^aR^b, -S(O)₂NR^aR^b, and -S(O)₂R^a;
 29 R^9 and R^{10} are independently selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆
 30 alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆
 31 hydroxyhaloalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈
 32 cycloalkyl, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, and -S(O)₂R^a;
 33 R^{11} is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl,
 34 C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl, C₁₋₄
 35 alkoxyC₁₋₄alkyl, C₃₋₈ cycloalkyl, -C(O)NR^cR^b, -S(O)₂NR^cR^b, -S(O)(=NH)R^c,
 36 -S(O)₂R^c and a 5- or 6-membered heterocyclic or heteroaryl ring having from 1-3
 37 heteroatoms as ring vertices selected from N, O, and S; wherein the heterocyclic or
 38 heteroaryl ring is optionally substituted with from one to three members
 39 independently selected from halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆
 40 alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl and C₁₋₄ alkoxyC₁₋₄
 41 alkyl;
 42 or R^9 and R^{10} are combined to form a 5-membered carbocyclic or heterocyclic ring or a 6-
 43 membered carbocyclic, heterocyclic or heteroaryl ring, which is optionally substituted
 44 with one or more substituents independently selected from R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} ,
 45 R^{18} and R^{19} , the heterocyclic or heteroaryl ring each have from 1-4 heteroatoms as
 46 ring vertices selected from N, O and S;
 47 or R^{10} and R^{11} are combined to form a 5- or 6-membered carbocyclic, heterocyclic or
 48 heteroaryl ring, which is optionally substituted with one or more substituents
 49 independently selected from R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} , the heterocyclic
 50 or heteroaryl ring each have from 1-4 heteroatoms as ring vertices selected from N, O
 51 and S;
 52 each of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} is independently selected from the group
 53 consisting of H, halogen, CN, OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄
 54 haloalkoxy, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl and -NR^aR^b; or two R^{12} , R^{13} , R^{14} ,
 55 R^{15} , R^{16} , R^{17} , R^{18} and R^{19} moieties on the same carbon atom combine to form an oxo
 56 group;

each R^a and R^b is independently selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkyl, C₁₋₈ haloalkoxy, and C₁₋₈ hydroxyalkyl and R^c, when present, is selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkyl, C₁₋₈ haloalkoxy, C₁₋₈ hydroxyalkyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, and 5- or 6- membered heteroaryl, the heterocycloalkyl or heteroaryl ring each have from 1-4 heteroatoms as ring vertices selected from N, O and S.

2. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein each of Y², Y³ and Y⁴ is CR²R³.

3. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein each of Y² and Y³ is CR²R³, and Y⁴ is a bond.

4. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof having Formula (II):



wherein

Z is N or CR⁶;

Y², Y³ and Y⁴ are each independently selected from the group consisting of CR²R³, NR⁴, O, SO₂, and a bond; and no more than one of Y², Y³ and Y⁴ is a bond;

W¹, W², and W³ are each independently selected from the group consisting of CR⁵ and N;

R¹ is selected from the group consisting of H, halogen, hydroxy, CN, NO₂, -NR^aR^b, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈ cycloalkyl, -S(O)₂R^a, -C(O)NR^aR^b, -S(O)(=NH)R^a, and -S(O)₂NR^aR^b;

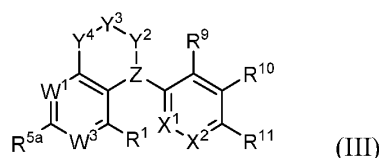
each R² and R³ are each independently selected from the group consisting of H, halogen, CN, NO₂, OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈ cycloalkyl, -S(O)₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, -S(O)(=NH)R^a, and -NR^aR^b;

each R⁴ is independently selected from H, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, and -C(O)R^a,

17 each R⁵ is independently selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl,
 18 C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈
 19 cycloalkyl, -S(O)₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, -S(O)(=NH)R^a,
 20 and -NR^aR^b;
 21 X¹ is N or CR^{8a};
 22 X² is N or CR^{8b};
 23 R^{8a} and R^{8b} are independently selected from the group consisting of H, halogen, CN, NH₂, NO₂,
 24 C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄
 25 alkyl, C₃₋₆ cycloalkyl, -C(O)NR^aR^b, -S(O)₂NR^aR^b, and -S(O)₂R^a;
 26 R⁹ and R¹⁰ are independently selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆
 27 alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆
 28 hydroxyhaloalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈
 29 cycloalkyl, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, and -S(O)₂R^a;
 30 R¹¹ is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆
 31 alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl, C₁₋₄ alkoxyC₁₋₄alkyl,
 32 C₃₋₈ cycloalkyl, -NR^cR^b, -C(O)NR^cR^b, -C(O)OH, -S(O)₂NR^cR^b, -S(O)(=NH)R^c, -S(O)₂R^c,
 33 phenyl, 5- to 6-membered heterocyclic or 5- to 10-membered heteroaryl ring, wherein the
 34 heterocyclic and heteroaryl rings have from 1-3 heteroatoms as ring vertices selected
 35 from N, O, and S; wherein the phenyl is optionally fused to a 5- or 6-membered
 36 heterocycle having from 1-2 heteroatoms as ring vertices selected from N, O, and S; and
 37 wherein the phenyl, heterocyclic or heteroaryl rings are optionally substituted with from
 38 one to three members independently selected from halogen, CN, NO₂, NH₂, C(O)NH₂,
 39 S(O)₂CH₃, -CH₂NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆
 40 hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl and C₁₋₄ alkoxyC₁₋₄alkyl; optionally wherein two
 41 members attached to the same carbon of the heterocyclic ring taken together form =CH₂
 42 or oxo (=O) group;
 43 or R⁹ and R¹⁰ are combined to form a 5-membered carbocyclic or heterocyclic ring or a 6-
 44 membered carbocyclic, heterocyclic or heteroaryl ring, which is optionally substituted
 45 with one or more substituents independently selected from R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸
 46 and R¹⁹, the heterocyclic or heteroaryl ring each have from 1-4 heteroatoms as ring
 47 vertices selected from N, O and S;

48 or R¹⁰ and R¹¹ are combined to form a 5- or 6-membered carbocyclic, heterocyclic or heteroaryl
 49 ring, which is optionally substituted with one or more substituents independently selected
 50 from R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹, the heterocyclic or heteroaryl ring each
 51 have from 1-4 heteroatoms as ring vertices selected from N, O and S;
 52 each of R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ is independently selected from the group
 53 consisting of H, halogen, CN, OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy,
 54 C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl and -NR^aR^b; or two R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷,
 55 R¹⁸ and R¹⁹ moieties on the same carbon atom combine to form an oxo group;
 56 each R^a and R^b is independently selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ alkoxy,
 57 C₁₋₈ haloalkyl, C₁₋₈ haloalkoxy, and C₁₋₈ hydroxyalkyl and
 58 R^c, when present, is selected from the group consisting of H, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈
 59 haloalkyl, C₁₋₈ haloalkoxy, C₁₋₈ hydroxyalkyl, C₃₋₆ cycloalkyl, 3- to 6-membered
 60 heterocycloalkyl, and 5- or 6- membered heteroaryl, wherein the heterocycloalkyl or
 61 heteroaryl ring each have from 1-4 heteroatoms as ring vertices selected from N, O and S.

1 5. The compound of claim 4, or a pharmaceutically acceptable salt thereof
 2 having Formula (III):

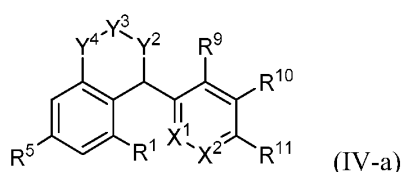


3 (III)
 4 wherein
 5 Y², Y³ and Y⁴ are each independently selected from the group consisting of CR²R³, NR⁴, SO₂, O
 6 and a bond; and no more than one of Y², Y³ and Y⁴ is a bond;
 7 W¹ and W³ are each independently selected from CH and N;
 8 Z is N or CR⁶;
 9 R¹ is selected from the group consisting of halogen and CN;
 10 each R² and R³ are each independently selected from the group consisting of H, halogen, CN,
 11 NH₂, NO₂, OH, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₁₋₃ hydroxyalkyl,
 12 C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₆

13 cycloalkyl, $-S(O)_2R^a$, $-CO_2R^a$, $-C(O)R^a$, $-C(O)NR^aR^b$, $-S(O)_2NR^aR^b$,
 14 $-S(O)(=NH)R^a$, and $-NR^aR^b$
 15 each R^4 is independently selected from H, C_{1-3} alkyl, C_{3-6} cycloalkyl, and $-C(O)R^a$;
 16 R^{5a} is selected from the group consisting of hydrogen, halogen, and CN;
 17 R^6 is H;
 18 X^1 is N or CR^{8a} ;
 19 X^2 is N or CR^{8b} ;
 20 R^{8a} and R^{8b} are independently selected from the group consisting of H, halogen, CN, NH_2 ,
 21 NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-3}
 22 alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl, $-C(O)NR^aR^b$, $-S(O)_2NR^aR^b$, and $-S(O)_2R^a$;
 23 R^9 and R^{10} are independently selected from the group consisting of H, halogen, CN, NO_2 , C_{1-}
 24 3 alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} hydroxyalkyl, C_{1-3}
 25 hydroxyhaloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-8}
 26 cycloalkyl, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-S(O)_2NR^aR^b$, and $-S(O)_2R^a$;
 27 R^{11} is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl,
 28 C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, C_{1-4}
 29 alkoxy C_{1-4} alkyl, C_{3-8} cycloalkyl, $-C(O)NR^cR^b$, -
 30 $C(O)OH$, $-S(O)_2NR^cR^b$, $-S(O)(=NH)R^c$,
 31 $-S(O)_2R^c$, phenyl, and a 5- or 6-membered heterocyclic or 5- to 10-membered
 32 heteroaryl ring, wherein the heterocyclic or heteroaryl ring has from 1-3 heteroatoms
 33 as ring vertices selected from N, O and S; wherein the phenyl is optionally fused to a
 34 5- or 6-membered heterocycle having from 1-2 heteroatoms as ring vertices selected
 35 from N, O, and S; and wherein the phenyl, heterocyclic or heteroaryl ring is
 36 optionally substituted with from one to three members independently selected from
 37 halogen, CN, NO_2 , NH_2 , $C(O)NH_2$, $S(O)_2CH_3$, $-CH_2NH_2$, C_{1-3} alkyl, C_{1-3} haloalkyl,
 38 C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} hydroxyalkyl, C_{1-3} hydroxyhaloalkyl and C_{1-3}
 39 alkoxy C_{1-4} alkyl; optionally wherein two members attached to the same carbon of the
 40 heterocyclic ring taken together form $=CH_2$ or oxo ($=O$) group;
 41 or R^9 and R^{10} are combined to form a 5-membered carbocyclic or heterocyclic ring or a 6-
 42 membered carbocyclic, heterocyclic or heteroaryl ring, which is optionally substituted
 43 with one or more substituents independently selected from R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} ,

44 R^{18} and R^{19} , the heterocyclic or heteroaryl ring each have from 1-4 heteroatoms as
 45 ring vertices selected from N, O and S;
 46 or R^{10} and R^{11} are combined to form a 5- or 6-membered carbocyclic, heterocyclic or
 47 heteroaryl ring, which is optionally substituted with one or more substituents
 48 independently selected from R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} , the heterocyclic
 49 or heteroaryl ring each have from 1-4 heteroatoms as ring vertices selected from N, O
 50 and S;
 51 each of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} is independently selected from the group
 52 consisting of H, halogen, CN, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4}
 53 haloalkoxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy C_{1-4} alkyl and $-NR^aR^b$; or two R^{12} , R^{13} , R^{14} ,
 54 R^{15} , R^{16} , R^{17} , R^{18} and R^{19} moieties on the same carbon atom combine to form an oxo
 55 group;
 56 each R^a and R^b is independently selected from the group consisting of H, C_{1-3} alkyl, C_{1-3} alkoxy,
 57 C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} hydroxyalkyl; and
 58 R^c , when present, is selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8}
 59 haloalkyl, C_{1-8} haloalkoxy, C_{1-8} hydroxyalkyl, C_{3-6} cycloalkyl, 3- to 6-membered
 60 heterocycloalkyl, and 5- or 6- membered heteroaryl, the heterocycloalkyl or heteroaryl
 61 ring each have from 1-4 heteroatoms as ring vertices selected from N, O and S.

1 **6.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (IV-a):



3
4 wherein

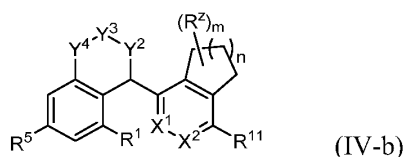
5 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR^2R^3 , NR^4 , SO_2 ,
 6 and a bond; and no more than one of Y^2 , Y^3 and Y^4 is a bond;

7 R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy,
 8 C_{1-4} haloalkoxy, $-S(O)_2R^a$ and $-C(O)NR^aR^b$;

9 each R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN,
 10 NO_2 , OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-4}
 11 alkoxy C_{1-4} alkyl, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$ and $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;
 12 each R^4 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-8} cycloalkyl,
 13 and $-\text{C}(\text{O})\text{R}^a$,
 14 each R^5 is independently selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl,
 15 C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$,
 16 and $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$.

1 7. The compound of claim 6, wherein X^1 and X^2 are independently selected
 2 from the group consisting of CH and N.

1 8. The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (IV-b):

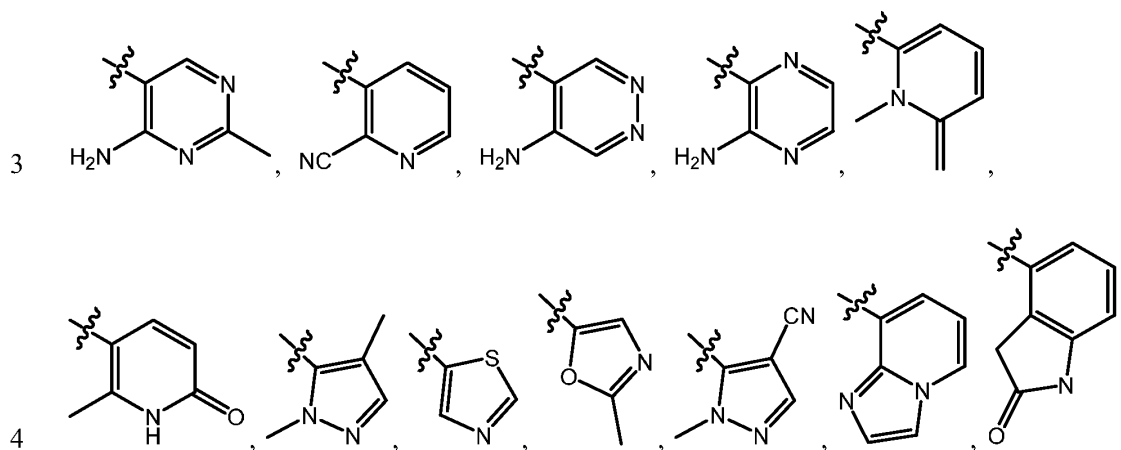


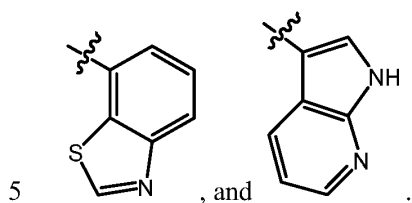
3
 4 wherein
 5 the subscript m is 1, 2, 3, 4, 5, 6, 7 or 8;
 6 the subscript n is 1 or 2;
 7 R^z represents one or more of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} ;
 8 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR^2R^3 , NR^4 , SO_2 ,
 9 and a bond; and no more than one of Y^2 , Y^3 and Y^4 is a bond;
 10 R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy,
 11 C_{1-4} haloalkoxy, $-\text{S}(\text{O})_2\text{R}^a$ and $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;
 12 each R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN,
 13 NO_2 , OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-4}
 14 alkoxy C_{1-4} alkyl, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$ and $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;
 15 each R^4 is independently selected from H, C_{1-6} alkyl, C_{3-8} cycloalkyl, and $-\text{C}(\text{O})\text{R}^a$;
 16 R^5 is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}
 17 alkoxy, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$; and

each of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} is independently selected from the group consisting of H, halogen, CN, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy C_{1-4} alkyl and $-NR^aR^b$; or two R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} moieties on the same carbon atom combine to form an oxo group.

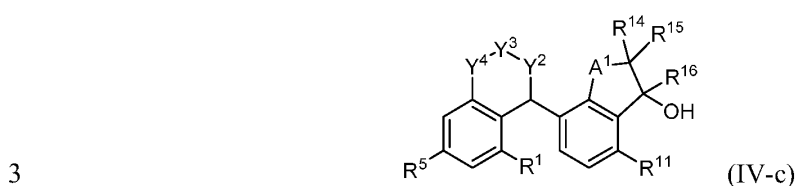
9. The compound of claim 8, wherein R^{11} is a phenyl, 5- or 6-membered heterocyclic, or 5- to 10-membered heteroaryl ring, wherein the heterocyclic or heteroaryl ring has from 1-3 heteroatoms as ring vertices selected from N, O, and S; wherein the phenyl is optionally fused to a 5- or 6-membered heterocycle having from 1-2 heteroatoms as ring vertices selected from N, O, and S; and wherein the phenyl, heterocyclic, or heteroaryl ring is optionally substituted with from one to three members independently selected from halogen, CN, NO_2 , NH_2 , $C(O)NH_2$, $S(O)_2CH_3$, $-CH_2NH_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl and C_{1-4} alkoxy C_{1-4} alkyl; optionally wherein two members attached to the same carbon of the heterocyclic ring taken together form $=CH_2$ or oxo ($=O$) group.

10. The compound of claim 9, wherein R^{11} is selected from the group consisting of:





1 **11.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
2 or solvate thereof having Formula (IV-c):



4 wherein

5 A^1 is O or CHR^{13} ;

6 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR^2R^3 , NR^4 , SO_2 ,
7 and a bond; and no more than one of Y^2 , Y^3 and Y^4 is a bond;

8 R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy,
9 C_{1-4} haloalkoxy, $-S(O)_2R^a$ and $-C(O)NR^aR^b$;

10 R^5 is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}
11 alkoxy, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, $-S(O)_2R^a$, $-C(O)NR^aR^b$, and $-S(O)_2NR^aR^b$;

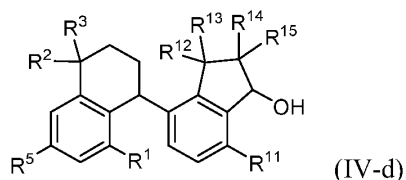
12 R^{11} is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}
13 alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, C_{1-4} alkoxy C_{1-4} alkyl,
14 C_{3-8} cycloalkyl, $-C(O)NR^cR^b$, $-S(O)_2NR^cR^b$, $-S(O)(=NH)R^c$, and $-S(O)_2R^c$;

15 each of R^{13} , R^{14} and R^{15} is independently selected from the group consisting of H, halogen, CN,
16 OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, C_{1-4}
17 alkoxy C_{1-4} alkyl and $-NR^aR^b$; and

18 R^{16} is selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} fluoroalkyl.

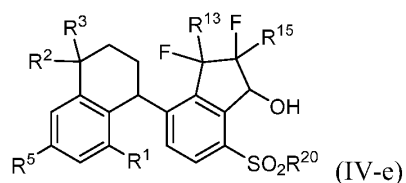
1 **12.** The compound of any one of claims 4-11, or a pharmaceutically
2 acceptable salt, hydrate, or solvate thereof, wherein Y^2 is CR^2R^3 , wherein each R^2 and R^3 is H;
3 and Y^3 and Y^4 are each CR^2R^3 , wherein each R^2 and R^3 are independently selected from H and F.

1 **13.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
2 or solvate thereof having Formula (IV-d):



4 wherein
5 R¹ is selected from the group consisting of halogen, CN, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄
6 alkoxy, -S(O)₂R^a and -C(O)NR^aR^b;
7 R² and R³ are each independently selected from the group consisting of H, halogen, CN, NO₂,
8 OH, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, C₁₋₆ alkoxy, C₁₋₆ fluoroalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄
9 alkoxyC₁₋₄alkyl and -NR^aR^b;
10 R⁵ is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, C₁₋₆
11 alkoxy, C₁₋₆ fluoroalkoxy, C₃₋₈ cycloalkyl, -S(O)₂R^a, -C(O)NR^aR^b, and -S(O)₂NR^aR^b;
12 R¹¹ is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl,
13 C₁₋₆ alkoxy, C₁₋₆ fluoroalkoxy, C₁₋₆ hydroxyfluoralkyl, C₃₋₈ cycloalkyl, -C(O)NR^cR^b,
14 -S(O)₂NR^cR^b, -S(O)(=NH)R^c, and -S(O)₂R^c;
15 each of R¹², R¹³, R¹⁴ and R¹⁵ is independently selected from the group consisting of H, halogen,
16 CN, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy and -NR^aR^b.

1 **14.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
2 or solvate thereof having Formula (IV-e):

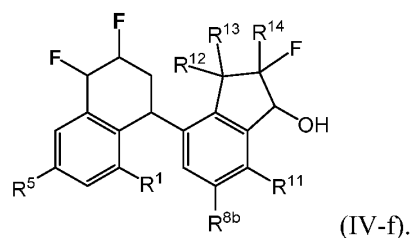


4 wherein
5 R¹ is selected from the group consisting of halogen, CN, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄
6 alkoxy, -S(O)₂R^a and -C(O)NR^aR^b;

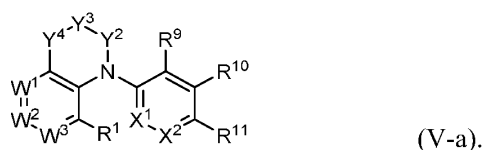
- 7 R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, NO₂,
 8 OH, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, C₁₋₆ alkoxy, C₁₋₆ fluoroalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄
 9 alkoxyC₁₋₄alkyl and -NR^aR^b;
 10 R^5 is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, C₁₋₆
 11 alkoxy, C₁₋₆ fluoroalkoxy, C₃₋₈ cycloalkyl, -S(O)₂R^a, -C(O)NR^aR^b, and -S(O)₂NR^aR^b;
 12 each of R^{13} and R^{15} is independently selected from the group consisting of H, F and C₁₋₄ alkyl;
 13 and
 14 R^{20} is selected from the group consisting of C₁₋₆ alkyl and C₁₋₆ fluoroalkyl.

- 1 **15.** The compound of claim 14, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof, wherein R^{20} is selected from the group consisting of methyl, fluoromethyl,
 3 difluoromethyl and trifluoromethyl.

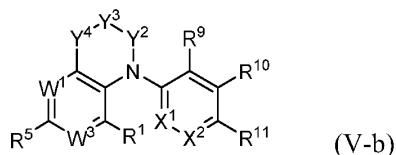
- 1 **16.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate
 2 or solvate thereof having Formula (IV-f):



- 1 **17.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (V-a):



- 1 **18.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (V-b):



3

4 wherein

5 each R^5 is independently selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl,
 6 C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈
 7 cycloalkyl, -S(O)₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, -S(O)(=NH)R^a,
 8 and -NR^aR^b.

1

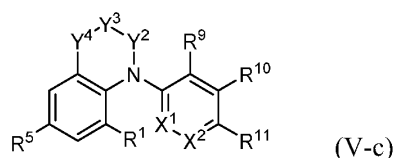
19. The compound of claim **18**, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof wherein R^9 and R^{10} are each independently selected from the group consisting
 3 of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆
 4 hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl, C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈
 5 cycloalkyl, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -S(O)₂NR^aR^b, and -S(O)₂R^a; and

6

R^{11} is selected from the group consisting of H, halogen, CN, NO₂, C₁₋₆ alkyl, C₁₋₆
 7 haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxyhaloalkyl,
 8 C₁₋₄ alkoxyC₁₋₄alkyl, C₃₋₈ cycloalkyl, -C(O)NR^cR^b, -S(O)₂NR^cR^b, and -S(O)₂R^c.

1

20. The compound of claim **4**, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (V-c):



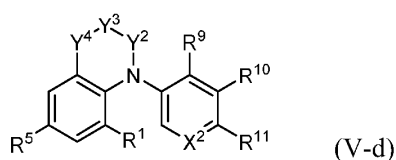
3

4 wherein

5 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR²R³, NR⁴, SO₂,
 6 and a bond; and no more than one of Y^2 , Y^3 and Y^4 is a bond;
 7 R^1 is selected from the group consisting of halogen, CN, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄
 8 alkoxy, -S(O)₂R^a and -C(O)NR^aR^b;

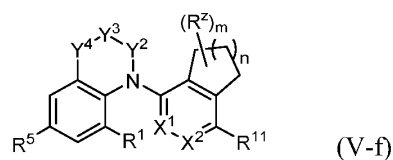
- 9 R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, NO_2 ,
 10 OH, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$,
 11 $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{NR}^a\text{R}^b$;
 12 R^5 is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6}
 13 alkoxy, C_{1-6} fluoroalkoxy, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$.

1 **21.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (V-d):



- 4 wherein
 5 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR^2R^3 and a bond;
 6 and no more than one of Y^2 , Y^3 and Y^4 is a bond;
 7 R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}
 8 alkoxy, $-\text{S}(\text{O})_2\text{R}^a$ and $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;
 9 R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, OH, C_{1-}
 10 C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, C_{1-4} alkoxy C_{1-}
 11 C_{1-4} alkyl, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{NR}^a\text{R}^b$; and
 12 R^5 is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6}
 13 alkoxy, C_{1-6} fluoroalkoxy, C_{3-8} cycloalkyl, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$.

1 **22.** The compound of claim 4, or a pharmaceutically acceptable salt, hydrate,
 2 or solvate thereof having Formula (V-f):



- 4 wherein
 5 the subscript m is 1, 2, 3, 4, 5, 6, 7 or 8;

6 the subscript n is 1 or 2;
 7 R^z represents one or more of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} ;
 8 Y^2 , Y^3 and Y^4 are each independently selected from the group consisting of CR^2R^3 , NR^4 , SO_2 ,
 9 and a bond; and no more than one of Y^2 , Y^3 and Y^4 is a bond;
 10 R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy,
 11 C_{1-4} haloalkoxy, $-S(O)_2R^a$ and $-C(O)NR^aR^b$;
 12 each R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN,
 13 NO_2 , OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-4}
 14 alkoxy C_{1-4} alkyl, C_{3-8} cycloalkyl, $-S(O)_2R^a$ and $-C(O)NR^aR^b$;
 15 each R^4 is independently selected from H, C_{1-6} alkyl, C_{3-8} cycloalkyl, and $-C(O)R^a$;
 16 R^5 is selected from the group consisting of H, halogen, CN, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}
 17 alkoxy, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, $-S(O)_2R^a$, $-C(O)NR^aR^b$, and $-S(O)_2NR^aR^b$; and
 18 each of R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} is independently selected from the group
 19 consisting of H, halogen, CN, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy,
 20 C_{1-4} hydroxyalkyl, C_{1-4} alkoxy C_{1-4} alkyl and $-NR^aR^b$; or two R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} ,
 21 R^{18} and R^{19} moieties on the same carbon atom combine to form an oxo group.

1 **23.** The compound of claim 4, selected from the compounds of Table 1, Table
 2 2, or Table 3.

1 **24.** A pharmaceutical composition comprising a compound of any one of
 2 claims **1-23** and a pharmaceutically acceptable excipient.

1 **25.** A method of treating a disease, disorder, or condition, mediated at least in
 2 part by HIF-2 α , said method comprising administering a therapeutically effective amount of a
 3 compound of any one of claims **1-23** to a subject in need thereof.

1 **26.** The method of claim **25**, wherein said compound is administered in an
 2 amount effective to reverse, slow or stop the progression of HIF-2 α -mediated dysregulation.

1 **27.** The method of any one of claims **25-26**, wherein said disease, disorder, or
 2 condition is cancer.

1 **28.** The method of claim **27**, wherein said cancer is a cancer of the prostate,
2 colon, rectum, pancreas, cervix, stomach, endometrium, uterus, brain, liver, bladder, ovary,
3 testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white
4 blood cell (including lymphoma and leukemia), esophagus, breast, muscle, connective tissue,
5 intestine, lung (including small-cell lung carcinoma and non-small-cell lung carcinoma), adrenal
6 gland, thyroid, kidney, or bone; or is glioblastoma, mesothelioma, renal cell carcinoma, gastric
7 carcinoma, sarcoma (including Kaposi's sarcoma), choriocarcinoma, cutaneous basocellular
8 carcinoma, or testicular seminoma.

1 **29.** The method of claim **27**, wherein said cancer is selected from the group
2 consisting of melanoma, colorectal cancer, pancreatic cancer, breast cancer, prostate cancer, lung
3 cancer, leukemia, a brain tumor, lymphoma, ovarian cancer, Kaposi's sarcoma, renal cell
4 carcinoma, head and neck cancer, esophageal cancer and urothelial carcinoma.

1 **30.** The method of any one of claims **25-26**, wherein said disease, disorder, or
2 condition is an immune-related disease, disorder or condition.

1 **31.** The method of claim **30**, wherein said immune-related disease, disorder,
2 or condition is selected from the group consisting of rheumatoid arthritis, kidney failure, lupus,
3 asthma, psoriasis, colitis, pancreatitis, allergies, fibrosis, anemia fibromyalgia, Alzheimer's
4 disease, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, osteoporosis,
5 Parkinson's disease, infections, Crohn's disease, ulcerative colitis, allergic contact dermatitis and
6 other eczemas, systemic sclerosis and multiple sclerosis.

1 **32.** The method of claim **25**, further comprising administering at least one
2 additional therapeutic agent.

1 **33.** The method of claim **32**, wherein said at least one additional therapeutic
2 agent is an immune checkpoint inhibitor.

1 **34.** The method of claim **33**, wherein said immune checkpoint inhibitor blocks
2 the activity of at least one of PD1, PD-L1, BTLA, LAG3, a B7 family member, TIM3, TIGIT or
3 CTLA4.

1 **35.** The method of claim **34**, wherein said immune checkpoint inhibitor blocks
2 the activity of PD1 or PD-L1.

1 **36.** The method of claim **35**, wherein said immune checkpoint inhibitor is
2 selected from the group consisting of nivolumab, pembrolizumab, avelumab, atezolizumab,
3 durvalumab, cemiplimab and zimberelimab.

1 **37.** The method of claim **34**, wherein said immune checkpoint inhibitor blocks
2 the activity of TIGIT.

1 **38.** The method of claim **37**, wherein said immune checkpoint inhibitor blocks
2 the activity of TIGIT by activating its ligand.

1 **39.** The method of any one of claims **34** to **38**, further comprising a
2 chemotherapeutic agent.

1 **40.** The method of any one of claims **34** to **39**, further comprising an A2R
2 antagonist.

1 **41.** The method of any one of claims **34** to **40**, further comprising a CD73
2 inhibitor.

1 **42.** The method of any one of claims **34** to **41**, further comprising radiation.

1 **43.** A combination comprising a compound of any one of claims **1-23**, and at
2 least one additional therapeutic agent.

1 **44.** The combination of claim **43**, wherein the at least one additional
2 therapeutic agent is an immune checkpoint inhibitor.

1 **45.** The combination of claim **44**, wherein said immune checkpoint inhibitor
2 blocks the activity of at least one of PD1, PD-L1, BTLA, LAG3, a B7 family member, TIM3,
3 TIGIT or CTLA4.

1 **46.** The combination of claim **45**, wherein said immune checkpoint inhibitor
2 blocks the activity of PD1 or PD-L1.

1 **47.** The combination of claim **45**, wherein said immune checkpoint inhibitor
2 blocks the activity of TIGIT.

1 **48.** The combination of claim **47**, wherein said immune checkpoint inhibitor
2 blocks the activity of TIGIT by activating its ligand.

1 **49.** The combination of any one of claims **46** to **48**, further comprising a
2 chemotherapeutic agent.

1 **50.** The combination of claim **49**, wherein the chemotherapeutic agent
2 comprises a platinum-based or anthracycline-based chemotherapeutic agent.

1 **51.** The combination of claim **50**, wherein the chemotherapeutic agent is
2 selected from the group consisting of cisplatin, carboplatin, oxaliplatin, doxorubicin, and
3 paclitaxel.

1 **52.** The combination of any one of claims **46** to **51**, further comprising an A₂R
2 antagonist.

1 **53.** The combination of any one of claims **46** to **52**, further comprising a
2 CD73 inhibitor.

1 **54.** The combination of any one of claims **46** to **53**, further comprising a
2 radiation.

1 **55.** The combination of claim **43**, wherein the at least one additional
2 therapeutic agent is a chemotherapeutic agent.

1 **56.** The combination of claim **55**, wherein the chemotherapeutic agent is a
2 platinum-based or anthracycline-based chemotherapeutic agent.

1 **57.** The combination of claim **56**, wherein the chemotherapeutic agent is
2 selected from the group consisting of cisplatin, carboplatin, oxaliplatin, doxorubicin and
3 paclitaxel.

1 **58.** The combination of claim **57**, further comprising an agent that targets the
2 extracellular production of adenosine.

1 **59.** The combination of claim **56** to **58**, further comprising radiation.

1 **60.** The combination of any one of claims **43** to **59**, wherein said compound
2 and said at least one additional therapeutic agent are administered in combination.

1 **61.** The combination of any one of claims **43** to **59**, wherein said compound
2 and said at least one additional therapeutic agent are administered sequentially.

1 **62.** The combination of any one of claims **43** to **59**, wherein the treatment
2 periods for the administration of the compound and the at least one additional therapeutic agent
3 overlap.