Claims:

1. A mitochondrial complex I modulator, MCIM, compound, for use in the treatment of an inflammatory and/or progressive disease in a subject in need thereof, wherein the compound is to be administered to the subject to achieve tissue repair and/or disease regression,

wherein the tissue repair and/or disease regression:

(i) comprises an increased repair score and/or increased wound healing;

(ii) comprises an increased cell count of reparative cells and/or a decrease in destructive cells;

(iii) induces a restoration of anatomically normal tissue architecture;

(iv) comprises a reduction in cytokine production from pro-inflammatory myeloid cells and/or peripheral mononuclear cells or lymphoid cells; and/or

(v) comprises increased bone formation and/or decreased bone resorption, optionally alongside reduced oedema and/or erythema, wherein the inflammatory and/or progressive disease is Rheumatoid Arthritis.

2. Use of a mitochondrial complex I modulator, MCIM, compound, in the manufacture of a medicament for the treatment of an inflammatory and/or progressive disease in a subject in need thereof, wherein the compound is to be administered to the subject to achieve tissue repair and/or disease regression,

wherein the tissue repair and/or disease regression:

(i) comprises an increased repair score and/or increased wound healing;

(ii) comprises an increased cell count of reparative cells and/or a decrease in destructive cells;

(iii) induces a restoration of anatomically normal tissue architecture;

(iv) comprises a reduction in cytokine production from pro-inflammatory myeloid cells and/or peripheral mononuclear cells or lymphoid cells; and/or

(v) comprises increased bone formation and/or decreased bone resorption, optionally alongside reduced oedema and/or erythema, wherein the inflammatory and/or progressive disease is Rheumatoid Arthritis.

3. The compound for use according to claim 1, or the use according to claim 2, wherein the tissue repair and/or disease regression comprises an increased cell count of reparative cells and the reparative cells comprise epithelial cells and/or mucus cells, and the inflammatory and/or progressive disease is an inflammatory bowel disease.

4. The compound for use according to claim 1, or the use according to claim 2, wherein the tissue repair and/or disease regression comprises an increased cell count of reparative cells and the reparative cells comprise alveolar type 1, type 2 cells and/or club cells, and the inflammatory and/or progressive disease is an interstitial lung disease and/or pulmonary fibrosis.

5. The compound for use according to claim 1, or the use according to claim 2, wherein the tissue repair and/or disease regression comprises an increased cell count of reparative cells and the reparative cells comprise oligodendrocyte precursor cells, and the inflammatory and/or progressive disease is multiple sclerosis.

6. The compound for use according to claim 1, or the use according to claim 2, wherein the tissue repair and/or disease regression comprises an increased cell count of reparative cells and the reparative cells comprise osteoblasts and/or non-transformed fibroblasts, and wherein the inflammatory and/or progressive disease is Rheumatoid Arthritis.

7. The compound for use according to any one of claims 1 and 3 to 6, or the use according to any one of claims 2 to 6, wherein:

(i) the binding of the compound to complex I modulates complex I activity, wherein complex I modulation is determined by detecting a reduction in cellular O_2 consumption without a reduction of cell viability; and/or

(ii) the binding of the compound to complex I modulates complex I activity, leading to a reversible reduction in cell proliferation.

8. The compound for use according to any one of claims 1 and 3 to 7, or the use according to any one of claims 2 to 7, wherein the compound interacts with complex I at a binding site outside the Q tunnel.

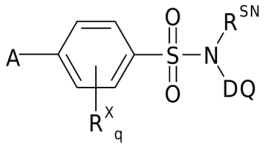
9. The compound for use according to any one of claims 1 and 3 to 8, or the use according to any one of claims 2 to 8, wherein the binding site comprises one or more amino acid residues from NDUSF2 and/or NDUSF7.

10. The compound for use, or the use according to claim 9, wherein the compound interacts with one or more amino acid residues in NDUFS2 selected from His92, Gly85, Tyr141, His88, Leu95, Asp193 and Phe458.

11. The compound for use, or the use according to claim 10, wherein the compound interacts with at least one amino acid residues in NDUFS2 selected from Tyr141, His92 and Asp139.

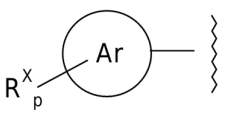
12. The compound for use according to any one of claims 1 and 3 to 11, or the use according to any one of claims 2 to 11, wherein a 3D conformation of the compound as annotated by *Molecular Operating Environment, MOE,* 2022 unified annotation scheme comprises 4 or more pharmacophore features which conform to the pharmacophore model represented in Figure 29, and Tables 8-A, 8-B and 8-C.

13. The compound for use according to any one of claims 1 and 3 to 12, or the use according to any one of claims 2 to 12, wherein the compound is a compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, of the following formula:



, wherein:

-A is independently:



-Ar is independently phenyl, pyridinyl, or pyrimidinyl; and

p is independently an integer from 0 to 3;

and wherein:

q is independently an integer from 0 to 3;

and wherein:

$-R^{SN}$ is independently -H or saturated aliphatic C_{1-4}alkyl;

and wherein:

-DQ is independently $-D^1-Q^1$ or $-D^2=O$;

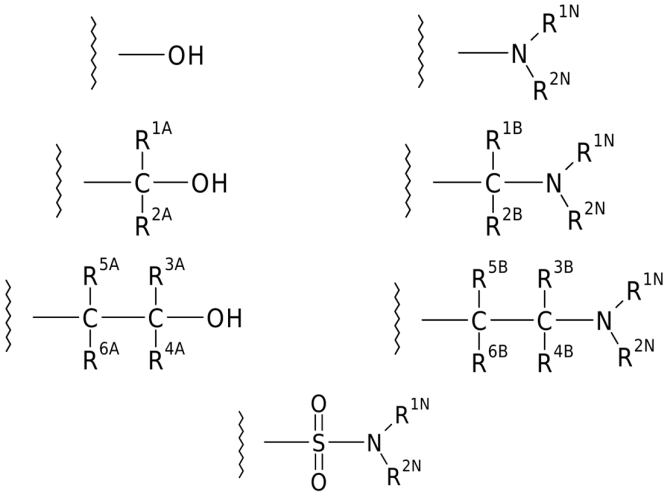
$-D^1-$ is independently cyclopentane-di-yl, cyclohexane-di-yl, cycloheptane-di-yl, bicyclo[3.1.1]heptane-di-yl, or bicyclo[3.2.1]octane-di-yl, and is optionally substituted with one or more groups $-R^D$;

$-D^2=$ is independently cyclopentane-yl-ylidene, cyclohexane-yl-ylidene, cycloheptane-yl-ylidene, bicyclo[3.1.1]heptane-yl-ylidene, or bicyclo[3.2.1]octane-yl-ylidene, and is optionally substituted with one or more groups $-R^D$;

each $-R^D$ is independently selected from -F, -Cl, -Br, -I, $-R^{DD}$, $-CF_3$, -OH, $-OR^{DD}$, $-NH_2$, $-NHR^{DD}$, and $-NR^{DD}_2$; and

each $-R^{DD}$ is independently saturated aliphatic C_{1-4}alkyl;

and wherein $-Q^1$ is independently selected from:



wherein:

each $-R^{1N}$ is independently -H, $-R^{CN}$, or $-R^{CF}$;

each $-R^{2N}$ is independently -H, $-R^{CN}$, or $-R^{CF}$;

each $-R^{CN}$ is independently saturated aliphatic C_{1-4}alkyl; and

each $-R^{CF}$, if present, is independently saturated aliphatic C_{1-4}fluoroalkyl;

or:

$-NR^{1N}R^{2N}$ is independently azetidino, pyrrolidino, imidazolidino, pyrazolidino, piperidino, piperazino, morpholino, thiomorpholino, azepino, or diazepino, each optionally substituted with one or more groups independently selected from saturated aliphatic C_{1-4}alkyl;

$-R^{1A}$ is independently -H, $-R^C$, or $-R^F$; and

$-R^{2A}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{1A}$ and $-R^{2A}$ together form a saturated aliphatic C_{2-4}alkylene group;

$-R^{1B}$ is independently -H, $-R^{C}$, or $-R^{F}$; and
$-R^{2B}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{1B}$ and $-R^{2B}$ together form a saturated aliphatic C_{2-4}alkylene group;
or $-R^{1B}$ and $-R^{2B}$ together form =O;

$-R^{3A}$ is independently -H, $-R^{C}$, or $-R^{F}$; and
$-R^{4A}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{3A}$ and $-R^{4A}$ together form a saturated aliphatic C_{2-4}alkylene group;

$-R^{5A}$ is independently -H, $-R^{C}$, $-R^{F}$, or $-R^{J}$; and
$-R^{6A}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{5A}$ and $-R^{6A}$ together form a saturated aliphatic C_{2-4}alkylene group;

$-R^{3B}$ is independently -H, $-R^{C}$, or $-R^{F}$; and
$-R^{4B}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{3B}$ and $-R^{4B}$ together form a saturated aliphatic C_{2-4}alkylene group;

$-R^{5B}$ is independently -H, $-R^{C}$, $-R^{F}$, -OH, or $-OR^{O}$; and
$-R^{6B}$ is independently -H, $-R^{C}$, or $-R^{F}$;
or $-R^{5B}$ and $-R^{6B}$ together form a saturated aliphatic C_{2-4}alkylene group;

each $-R^{C}$ is independently saturated aliphatic C_{1-4}alkyl;
each $-R^{F}$ is independently saturated aliphatic C_{1-4}fluoroalkyl;
$-R^{O}$ is independently saturated aliphatic C_{1-4}alkyl;
$-R^{J}$ is independently $-NH_2$, $-NHR^{JN1}$, $-NR^{JN1}{}_2$, or $-NR^{JN2}R^{JN3}$;
each $-R^{JN1}$ is independently saturated aliphatic C_{1-4}alkyl; and
$-NR^{JN2}R^{JN3}$ is independently azetidino, pyrrolidino, imidazolidino, pyrazolidino, piperidino, piperazino, morpholino, thiomorpholino, azepino, or diazepino, each optionally substituted with one or more groups independently selected from saturated aliphatic C_{1-4}alkyl;

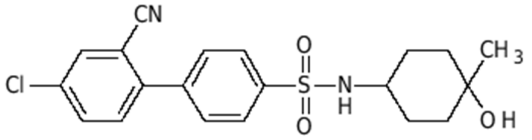
and wherein each $-R^{X}$ is independently:
-F, -Cl, -Br, -I,
$-R^{XX}$,
-OH, $-OR^{XX}$,
-SH, $-SR^{XX}$,
$-CF_3$, $-OCF_3$, $-SCF_3$,
$-NH_2$, $-NHR^{XX}$, $-NR^{XX}{}_2$, $-NR^{YY}R^{ZZ}$,
$-C(=O)R^{XX}$, $-OC(=O)R^{XX}$,
-C(=O)OH, $-C(=O)OR^{XX}$,
$-C(=O)NH_2$, $-C(=O)NHR^{XX}$, $-C(=O)NR^{XX}{}_2$, $-C(=O)NR^{YY}R^{ZZ}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{XX}$, $-OC(=O)NR^{XX}{}_2$, $-OC(=O)NR^{YY}R^{ZZ}$,
$-NHC(=O)R^{XX}$, $-NR^{XX}C(=O)R^{XX}$,
$-NHC(=O)OR^{XX}$, $-NR^{XX}C(=O)OR^{XX}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{XX}$, $-NHC(=O)NR^{XX}{}_2$, $-NHC(=O)NR^{YY}R^{ZZ}$,

$-NR^{XX}C(=O)NH_2$, $-NR^{XX}C(=O)NHR^{XX}$, $-NR^{XX}C(=O)NR^{XX}{}_2$, $-NR^{XX}C(=O)NR^{YY}R^{ZZ}$,
-CN,
$-NO_2$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{XX}$, $-S(=O)_2NR^{XX}{}_2$, $-S(=O)_2NR^{YY}R^{ZZ}$,
$-S(=O)R^{XX}$, $-S(=O)_2R^{XX}$, $-OS(=O)_2R^{XX}$, $-S(=O)_2OH$, or $-S(=O)_2OR^{XX}$;
wherein:

each $-R^{XX}$ is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl, wherein said phenyl and benzyl are optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, $-CF_3$, $-OCF_3$, $-R^{XXX}$, -OH, $-OR^{XXX}$, or $-SR^{XXX}$, wherein each $-R^{XXX}$ is independently saturated aliphatic C_{1-4}alkyl; and

each $-NR^{YY}R^{ZZ}$ is independently azetidino, pyrrolidino, imidazolidino, pyrazolidino, piperidino, piperazino, morpholino, thiomorpholino, azepino, or diazepino, each optionally substituted with one or more groups independently selected from saturated aliphatic C_{1-4}alkyl.

14. The compound for use, or the use according to claim 13, wherein the compound is a compound selected from compounds of the following formulae, or a pharmaceutically acceptable salt, hydrate, or solvate thereof:



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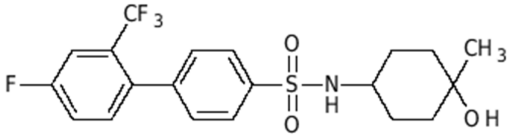

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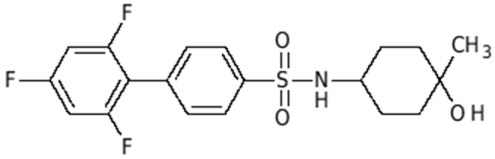

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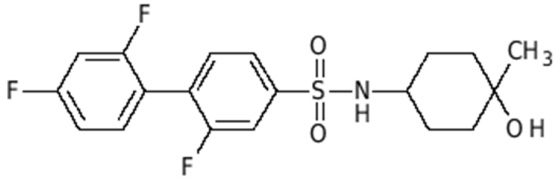

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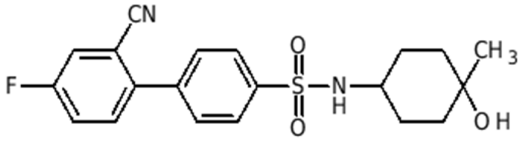

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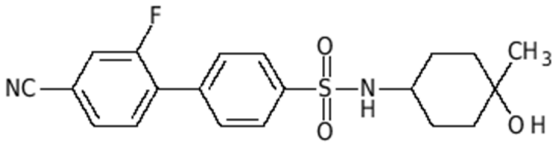
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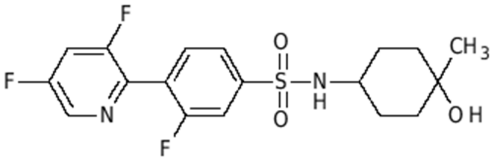
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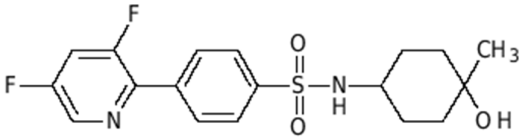
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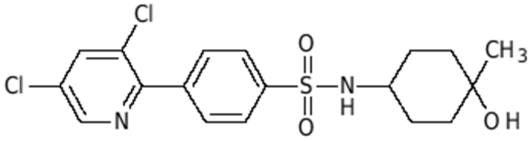
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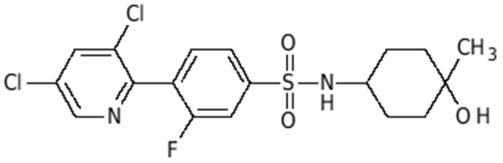
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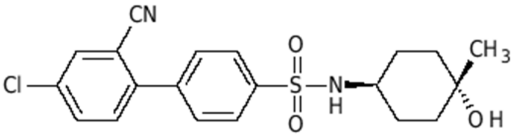
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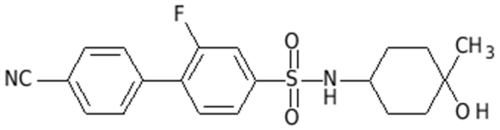
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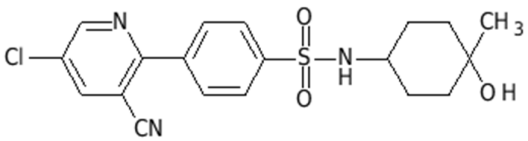
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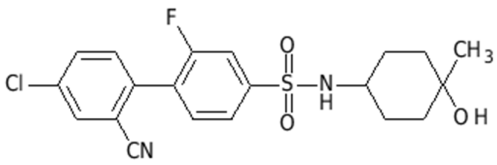
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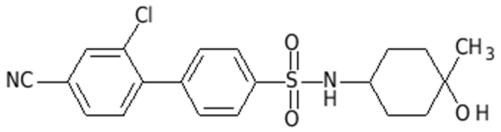
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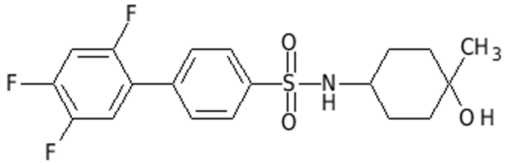
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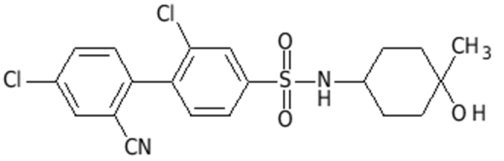
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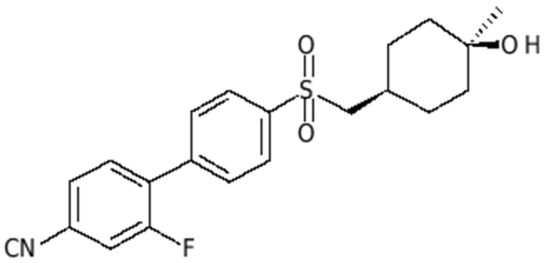
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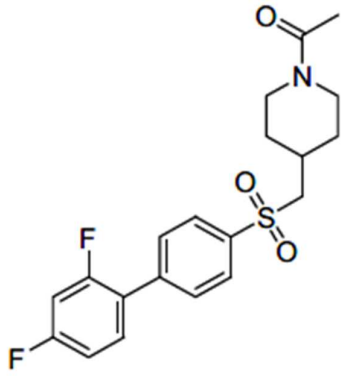
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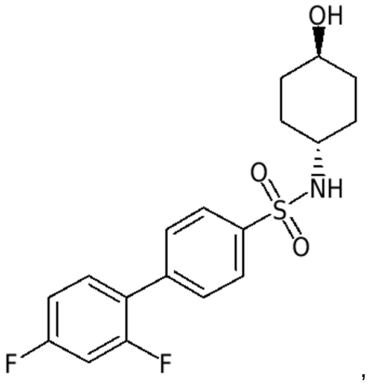
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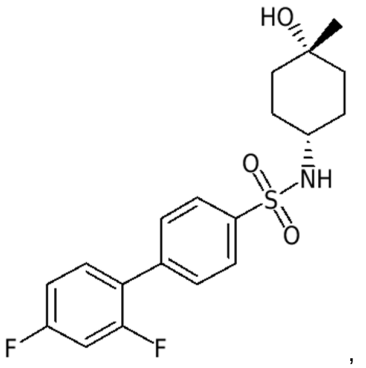

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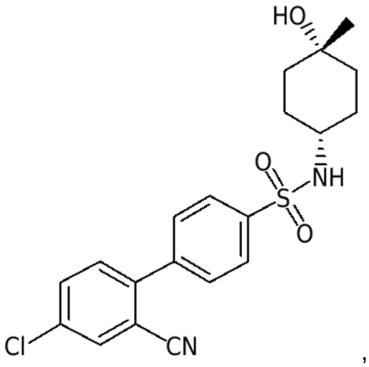

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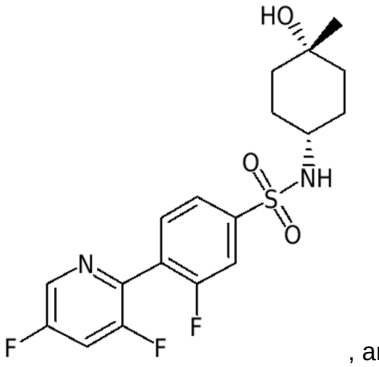

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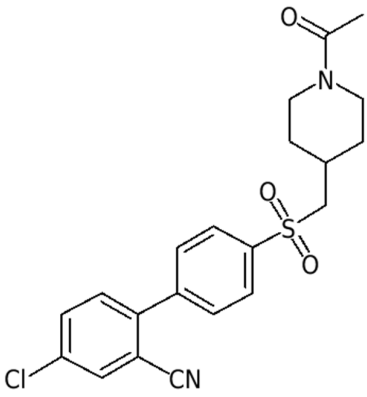

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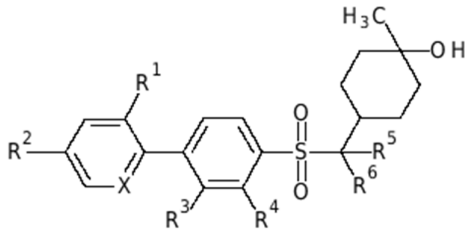
15. The compound for use according to any one of claims 1 and 3 to 12, or the use according to any one of claims 2 to 12, wherein the compound is a compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, of the following formula:



, wherein:

=X- is independently -CH= or -N=;

-R^1 is independently -H or -R^{1X};
-R^{1X} is independently -F, -Cl, -R^{1C}, -R^{1F}, or -CN;
-R^{1C} is independently saturated linear or branched C_{1-3}alkyl;
-R^{1F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^2 is independently -H or -R^{2X};
-R^{2X} is independently -F, -Cl, -R^{2C}, -R^{2F}, or -CN;
-R^{2C} is independently saturated linear or branched C_{1-3}alkyl;
-R^{2F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^3 is independently -H or -R^{3X};
-R^{3X} is independently -F, -Cl, -R^{3C}, -R^{3F}, or -CN;
-R^{3C} is independently saturated linear or branched C_{1-3}alkyl;
-R^{3F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

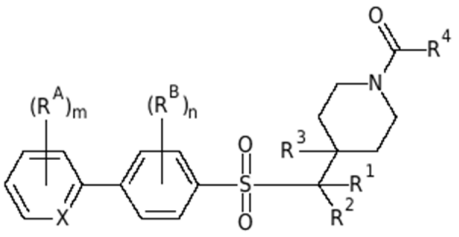
-R^4 is independently -H or -R^{4X};
-R^{4X} is independently -F, -Cl, -R^{4C}, -R^{4F}, or -CN;
-R^{4C} is independently saturated linear or branched C_{1-3}alkyl;
-R^{4F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^5 is independently -H or -R^{5X};
-R^{5X} is independently -F, -R^{5C}, or -R^{5F};
-R^{5C} is independently saturated linear or branched C_{1-3}alkyl;
-R^{5F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^6 is independently -H or -R^{6X};
-R^{6X} is independently -F, -R^{6C}, or -R^{6F};
-R^{6C} is independently saturated linear or branched C_{1-3}alkyl; and
-R^{6F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

or -R^5 and -R^6, taken together with the carbon atom to which they are attached, form saturated C_{3-6}cycloalkyl.

16. The compound for use according to any one of claims 1 and 3 to 12, or the use according to any one of claims 2 to 12, wherein the compound is a compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, of the following formula:



, wherein:

-X= is independently -CH= or -N=;

"m" is independently 0, 1, 2, or 3;

each -R^A is independently -F, -Cl, -R^{AC}, -R^{AF}, or -CN;

-R^{AC} is independently saturated linear or branched C_{1-3}alkyl;

-R^{AF} is independently saturated linear or branched C_{1-3}fluoroalkyl;

"n" is independently 0, 1, or 2;

each -R^B is independently -F, -Cl, -R^{BC}, -R^{BF}, or -CN;

-R^{BC} is independently saturated linear or branched C_{1-3}alkyl;

-R^{BF} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^1 is independently -H or -R^{1X};

-R^{1X} is independently -F, -R^{1C}, or -R^{1F};

-R^{1C} is independently saturated linear or branched C_{1-3}alkyl;

-R^{1F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^2 is independently -H or -R^{2X};

-R^{2X} is independently -F, -R^{2C}, or -R^{2F};

-R^{2C} is independently saturated linear or branched C_{1-3}alkyl;

-R^{2F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

or -R^1 and -R^2, taken together with the carbon atom to which they are attached, form saturated C_{3-6}cycloalkyl;

-R^3 is independently -H or -R^{3X};

-R^{3X} is independently -R^{3C} or -R^{3F};

-R^{3C} is independently saturated linear or branched C_{1-3}alkyl;

-R^{3F} is independently saturated linear or branched C_{1-3}fluoroalkyl;

-R^4 is independently -R^{4C}, -R^{4CC}, or -N(R^{4N1})(R^{4N2});

-R^{4C} is independently saturated linear or branched C_{1-6}alkyl;

-R^{4CC} is independently saturated C_{3-6}cycloalkyl;

-R^{4N1} is independently -H or -R^{4N1C};

-R^{4N1C} is independently saturated linear or branched C_{1-4}alkyl;

-R^{4N2} is independently -H or -R^{4N2C}; and

-R^{4N2C} is independently saturated linear or branched C_{1-4}alkyl,

or -N(R^{4N1})(R^{4N2}) is independently azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is optionally substituted with one or more saturated linear or branched C_{1-4}alkyl groups.