ISOQUINOLINE COMPOUNDS AND THEIR USE IN TREATING AhR IMBALANCE

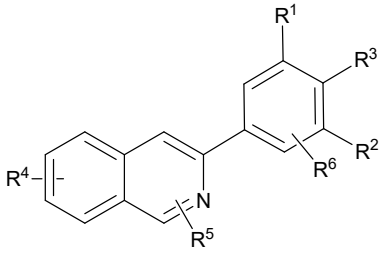
CROSS REFERENCE TO RELATED APPLICATION

[0001] The present application claims benefit of and priority to U.S. Provisional No. 63/052,561 entitled "ISOQUINOLINE COMPOUNDS AND THEIR USE IN TREATING AhR IMBALANCE," filed July 16, 2020; and U.S. Provisional No. 63/052,574 entitled "ISOQUINOLINE COMPOUNDS AND THEIR USE IN TREATING AhR IMBALANCE," filed July 16, 2020; the contents of which are hereby incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

[0002] The present disclosure provides compounds and compositions, and methods for the treatment and prevention of conditions associated with AhR imbalance, AhR mediated diseases and inflammatory disorders comprising administering such compounds and compositions. Compounds described herein bind and activates the Aryl hydrocarbon Receptor (AhR), providing a novel class of anti-inflammatory compounds with AhR-dependent cytokine modulation useful for the treatment of inflammatory disease states.

[0003] Some examples disclosed herein are directed to a compound of Formula (I) or a salt, solvate or hydrate thereof



(I)

wherein

each of R^1 and R^2 is independently selected from the group consisting of OH, OR^7, and H, provided that at least one of R^1 and R^2 is -OH or -OR^7;

R^7 is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, aryl C_{1-6} alkyl and acyl;

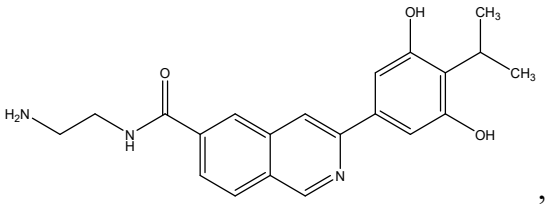
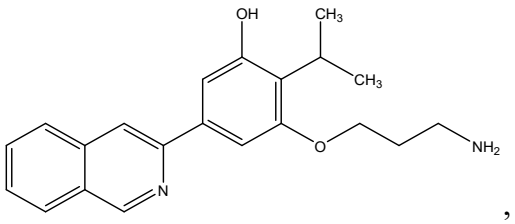
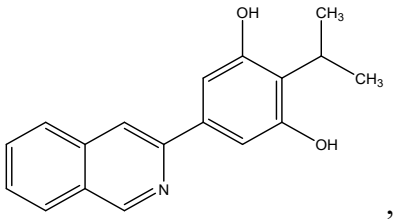
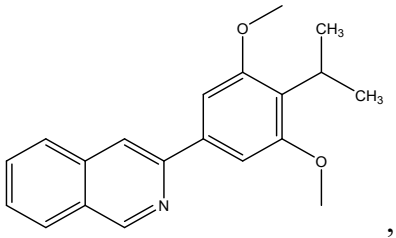
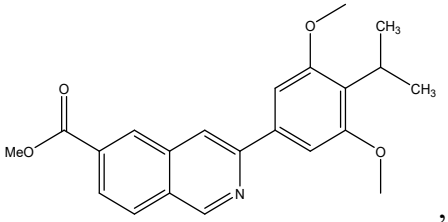
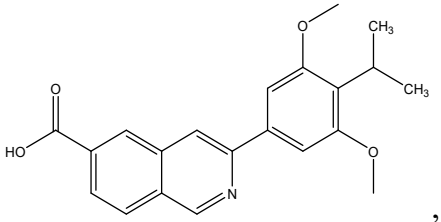
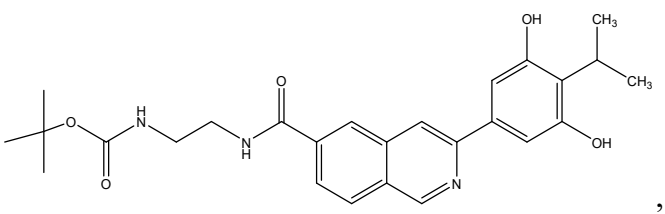
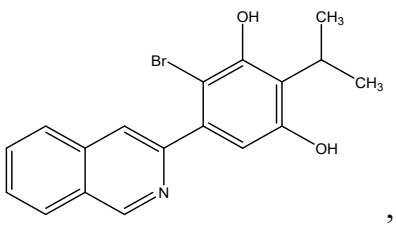
R^3 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl,

alternatively R^{15} and R^{16} together with the nitrogen to which they are attached, form a 5-7 membered cyclic saturated or unsaturated ring;

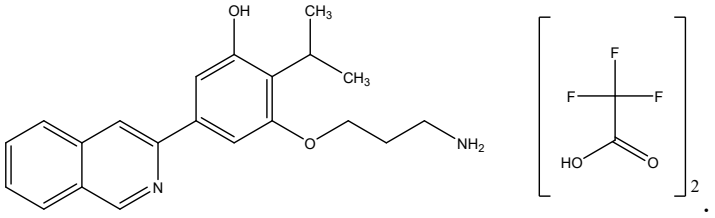
R^4 is selected from the group consisting of H, halo, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, $-(CR^{18}R^{19})_tCOOR^8$, $-(CR^{18}R^{19})_tOC(O)R^8$, $-(CR^{18}R^{19})_tNR^9R^{10}$, $-(CR^{18}R^{19})_tC(O)NR^9R^{10}$, $-(CR^{18}R^{19})_tNR^9C(O)R^8$, $-(CR^{18}R^{19})_tS(O)_2NR^9R^{10}$, $-(CR^{18}R^{19})_tCOR^{11}$, $-(CR^{18}R^{19})_tCH(O)$, $-(CR^{18}R^{19})_tOR^{12}$, $-(CR^{18}R^{19})_tS(O)_sR^{13}$, optionally substituted heterocyclic, and optionally substituted heterocyclic C_{1-6} alkyl; and

each of R^{18} and R^{19} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6} alkyl.

[0004] Some examples are directed to a compound selected from the group consisting of :

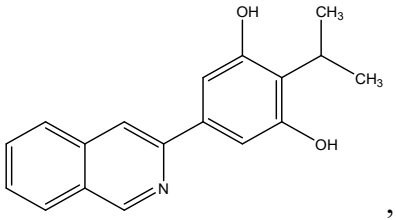

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, and

, or a salt, solvate or hydrate thereof.

[0005] Some examples are directed to a compound of the formula



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[0006] Some examples are directed to a compound of the formula

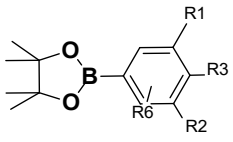


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or a pharmaceutically acceptable salt, solvate of hydrate thereof.

[0007] Some examples are directed to 2-isopropyl-5-(isoquinolin-3-yl)benzene-1,3-diol, or a pharmaceutically acceptable salt solvate of hydrate thereof.

[0008] Some examples describe a compound of Formula (II) or a salt solvate or hydrate thereof:



(II)

wherein

each R^1 and R^2 is independently selected from the group consisting of OH, OR^7, and H, provided that at least one of R^1 and R^2 is OH or OR^7;

R^7 is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, and acyl;

R^3 is selected from optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{4-6} cycloalkenyl, halo, cyano, $-C(O)OR^8$, $-NR^9R^{10}$, $-S(O)_2NR^9R^{10}$, $-C(O)R^{11}$, $-OR^{12}$, $-S(O)_n R^{13}$ and optionally substituted heterocyclic ring;

n is an integer having a value of 0, 1 or 2;

R^6 is H;

R^8 is selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6} alkyl;

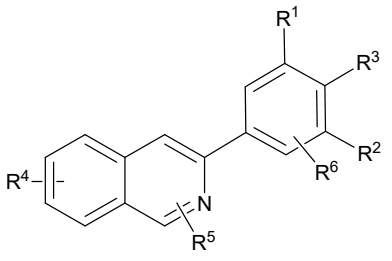
each of R^9 and R^{10} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6} alkyl; alternatively, R^9 and R^{10} together with the nitrogen atom to which they are attached, form a 5-7 membered cyclic saturated or unsaturated ring;

R^{11} is selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl; $-NR^9R^{10}$, and $-OR^{12}$;

each of R^{12} and R^{13} is independently is selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, and optionally substituted C_{3-6} cycloalkyl; and

R^6 is selected from the group consisting of halo, hydroxyl, alkoxy, optionally substituted C_{1-6} alkyl, halogenated alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted aryl C_{1-6} alkyl.

[0008a] In one aspect, the present disclosure provides a compound of Formula (I), or a salt, solvate or hydrate thereof



(I)

wherein

R^1 is selected from the group consisting of OH and OR^7, wherein R^7 is optionally substituted C_{1-6} alkyl;

R^2 is selected from the group consisting of OH and OR^7, wherein R^7 is optionally substituted C_{1-6} alkyl;

R^3 is optionally substituted C_{1-6} alkyl;

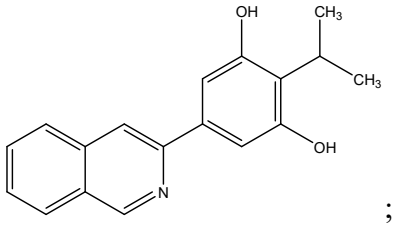
R^4 is selected from the group consisting of H, $-(CR^{18}R^{19})_tCOOR^8$, and $-(CR^{18}R^{19})_tC(O)NR^9R^{10}$; wherein t is 0, R^8 is selected from the group consisting of H and optionally substituted C_{1-6} alkyl, R^9 is H and R^{10} is optionally substituted C_{1-6} alkyl;

R^5 is H; and

R^6 is selected from the group consisting of H and halo.

[0008b] In another aspect, the present disclosure provides a compound which is 2-isopropyl-5-(isoquinolin-3-yl)benzene-1,3-diol, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0008c] In another aspect, the present dislcosure provides a compound of the formula:



;

or a salt, solvate or hydrate thereof.

[0009] Some examples herein describe a pharmaceutical composition comprising: a compound according to any example described herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and a pharmaceutically acceptable carrier or diluent. In one aspect, the present disclosure provides a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier or diluent.

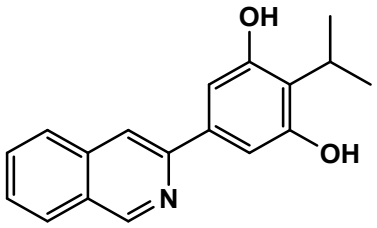
[0010] Some examples describe a method of treating or preventing a condition in a mammal associated with AhR imbalance, comprising administering to the mammal a therapeutically effective amount of any compound or pharmaceutical composition described herein. In one aspect, the present disclosure provides use of the compound as defined herein or the pharmaceutical composition as defined herein in the manufacture of a medicament for treating or preventing a condition in a mammal associated with AhR imbalance, wherein an effective amount of the compound or the pharmaceutical composition is to be administered to said mammal.

[0011] Some examples describe a method of treating or preventing an inflammatory disorder in a subject, comprising administering to the subject a therapeutically effective amount of any compound or pharmaceutical composition described herein. In some examples the inflammatory disorder is selected from the group consisting of psoriasis, atopic dermatitis, vitiligo, acne, neovascular (dry) AMD, neovascular (wet) AMD, uveitis or other inflammatory eye conditions, radiation dermatitis, COPD, asthma, multiple sclerosis (MS), and inflammatory bowel disease. In one aspect, the present disclosure provides use of the compound as defined herein or the pharmaceutical composition as defined herein in the manufacture of a medicament for treating or preventing an inflammatory disorder in a subject, wherein an effective amount is to be administered to said subject in need thereof. In some examples the inflammatory disorder is

psoriasis or atopic dermatitis. In some examples the compound or a pharmaceutical composition described herein is administered topically. In another aspect, the present disclosure provides use of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof, as defined herein in the manufacture of a medicament for treating or preventing psoriasis or atopic dermatitis in a subject, wherein an effective amount of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof is to be administered to the subject in need thereof.

[0012] Some examples describe a method of treating or preventing psoriasis or atopic dermatitis in a subject in need thereof, comprising administering to the subject an effective amount of 2-isopropyl-5-(isoquinolin-3-yl)benzene-1,3-diol, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0012a] In one aspect, the present disclosure provides a process for preparing a compound of Formula 8

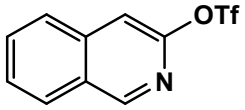


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or a pharmaceutically acceptable salt, solvate or hydrate thereof,

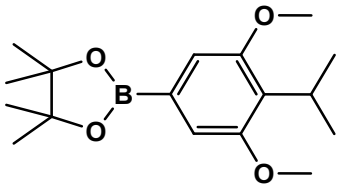
comprising:

a) coupling a compound of Formula 6



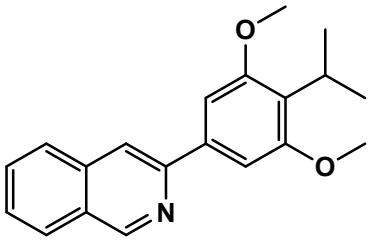
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or a pharmaceutically acceptable salt thereof with a compound of Formula 5



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or a pharmaceutically acceptable salt thereof to form a compound of Formula 7

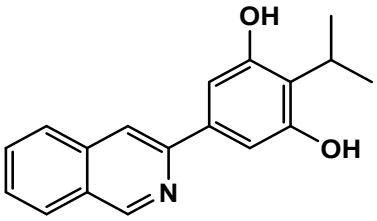


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or a pharmaceutically acceptable salt thereof; and

b) demethylating the compound of Formula 7 to form the compound of Formula 8, and optionally converting the compound of Formula 8 to a pharmaceutically acceptable salt, solvate or hydrate thereof.

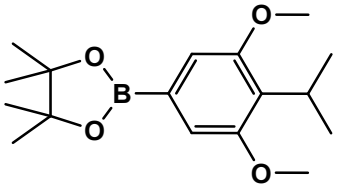
[0013] In another aspect, the present disclosure describe a process for preparing a compound of Formula 8



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or a pharmaceutically acceptable salt, solvate or hydrate thereof, comprising:

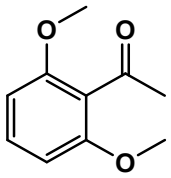
a) preparing a compound of Formula 5



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or a pharmaceutically acceptable salt, solvate or hydrate thereof, comprising

1) alkylating 2,6-dihydroxyacetophenone or a pharmaceutically acceptable salt, solvate or hydrate thereof, to form a compound of Formula 2



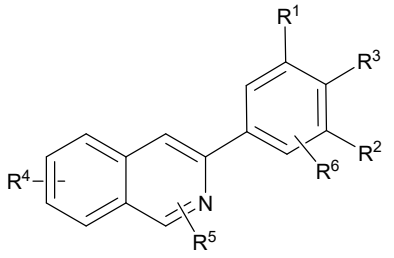
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or a pharmaceutically acceptable salt, solvate or hydrate thereof;

2) treating the ketone of Formula 2 or a pharmaceutically acceptable salt, solvate or hydrate thereof with a Grignard reagent, followed by elimination of water under acidic conditions to form a compound of Formula 3

What is claimed is:

1. A compound of Formula (I), or a salt, solvate or hydrate thereof



(I)

wherein

R^1 is selected from the group consisting of OH and OR^7, wherein R^7 is optionally substituted C_{1-6} alkyl;

R^2 is selected from the group consisting of OH and OR^7, wherein R^7 is optionally substituted C_{1-6} alkyl;

R^3 is optionally substituted C_{1-6} alkyl;

R^4 is selected from the group consisting of H, $-(CR^{18}R^{19})_tCOOR^8$, and $-(CR^{18}R^{19})_tC(O)NR^9R^{10}$; wherein t is 0, R^8 is selected from the group consisting of H and optionally substituted C_{1-6} alkyl, R^9 is H and R^{10} is optionally substituted C_{1-6} alkyl;

R^5 is H; and

R^6 is selected from the group consisting of H and halo.

2. The compound according to claim 1 wherein:

R^1 is selected from the group consisting of OH and OR^7, wherein R^7 is C_{1-6} alkyl;

R^2 is selected from the group consisting of OH and OR^7, wherein R^7 is C_{1-6} alkyl substituted with $NR^{22}R^{23}$, wherein R^{22} and R^{23} are independently selected from H and C_{1-3} alkyl; and

R^4 is selected from the group consisting of H, -COOH, $-COOCH_3$, and $-C(O)NR^9R^{10}$; wherein R^9 is H and R^{10} is selected from the group consisting of amino substituted C_{1-6} alkyl and $–(CH_2)_2NHC(O)O$-*t*-butyl.

3. The compound according to claim 1 wherein:

R^1 is selected from the group consisting of OH and $-OCH_3$;

R^2 is selected from the group consisting of OH, $-OCH_3$ and $-O-(CH_2)_3NH_2$;

R^3 is C_{1-6} alkyl;

R^4 is selected from the group consisting of H, $-COOH$, $-COOCH_3$, $-C(O)NH(CH_2)_2NH_2$; and $-C(O)NH(CH_2)_2NHC(O)O$-*t*-butyl; and

R^6 is selected from the group consisting of H and bromo.

4. The compound according to any one of claims 1-3, wherein R^3 is isopropyl or *t*-butyl.

5. The compound according to claim 1, wherein

R^1 is selected from the group consisting of OH and $-OCH_3$;

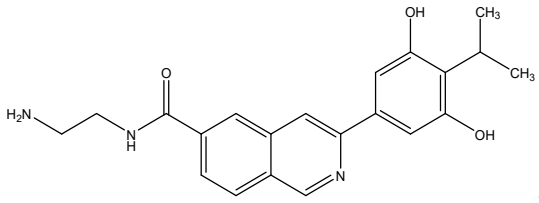
R^2 is selected from the group consisting of OH, $-OCH_3$ and $–O-(CH_2)_3NH_2$;

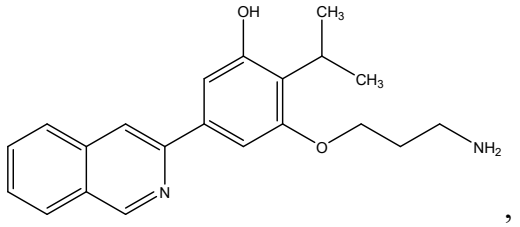
R^3 is isopropyl;

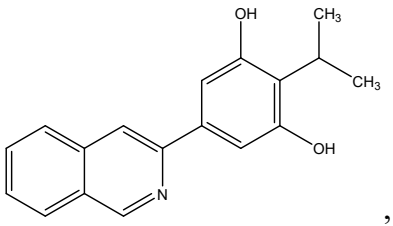
R^4 is selected from the group consisting of H, $-COOH$, $-COOCH_3$, $-C(O)(CH_2)_2NH_2$; and $-C(O)NH(CH_2)_2NHC(O)O$-*t*-butyl;

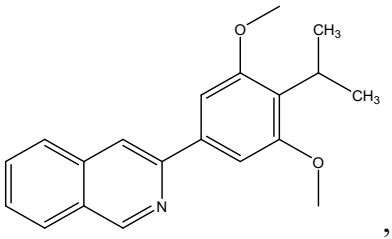
R^6 is selected from the group consisting of H and bromo.

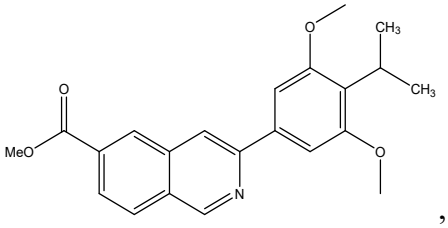
6. A compound selected from the group consisting of:

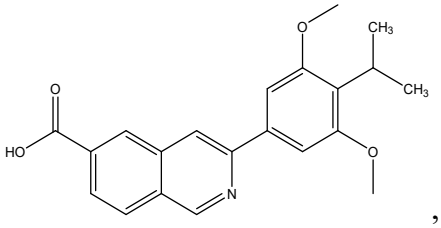


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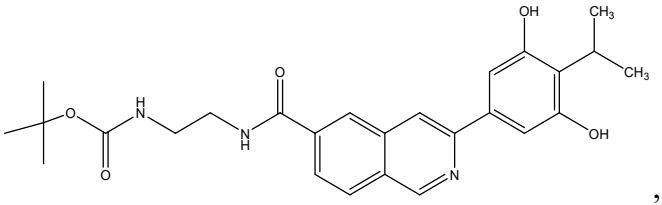
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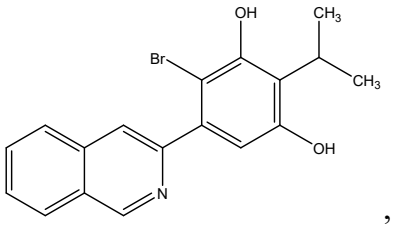
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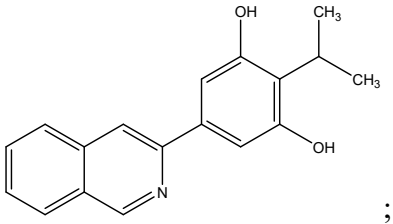


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, or a salt, solvate or hydrate thereof.

7. A compound which is 2-isopropyl-5-(isoquinolin-3-yl)benzene-1,3-diol, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

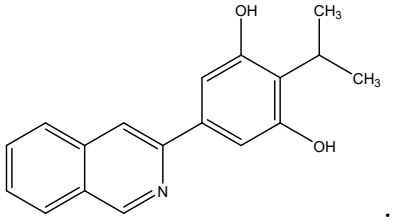
8. A compound of the formula:



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or a salt, solvate or hydrate thereof.

9. The compound of claim 4 that is



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10. A compound of claim 8 that is at least 90% pure by weight.

11. A compound of claim 8 that is at least 95% pure by weight.

12. A compound of claim 8 that is at least 98% pure by weight.

13. A compound of claim 8 that is at least 99% pure by weight.

14. A pharmaceutical composition comprising a compound according to claim 1 to 6 and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound according to any one of claim 7 to 13 and a pharmaceutically acceptable carrier or diluent.

16. The pharmaceutical composition of claim 15, wherein the carrier or diluent is suitable for oral, topical, parenteral, transdermal, intranasal or oral inhalation administration.

17. Use of the compound according to claim 1 to 6 or the pharmaceutical composition according to any one of claims 14 to 16 in the manufacture of a medicament for treating or preventing a condition in a mammal associated with AhR imbalance, wherein an effective amount of the compound or the pharmaceutical composition is to be administered to said mammal.

18. nUse of the compound according to claim 1 to 6 or the pharmaceutical composition according to any one of claims 14 to 16 in the manufacture of a medicament for treating or preventing an inflammatory disorder in a subject, wherein an effective amount is to be administered to said subject in need thereof.

19. The use according to claim 18 wherein the inflammatory disorder is selected from the group consisting of psoriasis, atopic dermatitis, vitiligo, acne, neovascular (dry) AMD, neovascular (wet) AMD, uveitis or other inflammatory eye conditions, radiation dermatitis, COPD, asthma, multiple sclerosis (MS), and inflammatory bowel disease.

20. Use of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof, according to any one of claims 7 to 13 in the manufacture of a medicament for treating or preventing an inflammatory disorder in a subject, wherein an effective amount of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof is to be administered to said subject in need thereof.

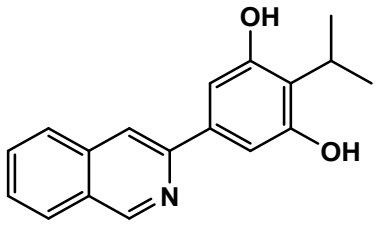
21. The use according to claim 20 wherein the inflammatory disorder is selected from the group consisting of psoriasis, atopic dermatitis, vitiligo, acne, neovascular (dry) AMD, neovascular (wet) AMD, uveitis or other inflammatory eye conditions, radiation dermatitis, COPD, asthma, multiple sclerosis (MS), and inflammatory bowel disease.

22. The use according to claim 20 wherein the inflammatory disorder is selected from the group consisting of psoriasis, atopic dermatitis, vitiligo, acne, uveitis, radiation dermatitis, COPD, asthma, multiple sclerosis (MS), and inflammatory bowel disease.

23. Use of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof, according to any one of claims 7 to 13 in the manufacture of a medicament for treating or preventing psoriasis or atopic dermatitis in a subject, wherein an effective amount of the compound or the pharmaceutically acceptable, salt, solvate or hydrate thereof is to be administered to the subject in need thereof.

24. The use according to claim 20 wherein the compound or the pharmaceutically acceptable salt, solvate or hydrate thereof, is to be administered orally, topically, parenterally, transdermally, intranasally, or by oral inhalation.

25. A process for preparing a compound of Formula 8

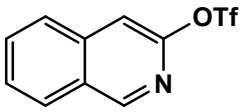


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or a pharmaceutically acceptable salt, solvate or hydrate thereof,

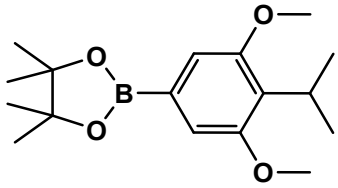
comprising:

a) coupling a compound of Formula 6

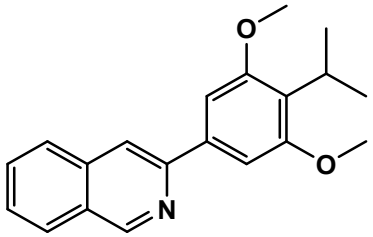


6,

or a pharmaceutically acceptable salt thereof with a compound of Formula 5



or a pharmaceutically acceptable salt thereof to form a compound of Formula 7



7

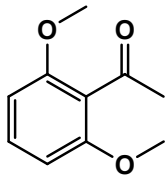
or a pharmaceutically acceptable salt thereof; and

b) demethylating the compound of Formula 7 to form the compound of Formula 8, and optionally converting the compound of Formula 8 to a pharmaceutically acceptable salt, solvate or hydrate thereof.

26. The process of claim 25 wherein the compound of Formula 6 or a pharmaceutically acceptable salt thereof, is prepared by treating isoquinoline-3-ol with a triflating agent.

27. The process of claim 25 wherein the compound of Formula 5 or a pharmaceutically acceptable salt thereof, is prepared by a process comprising:

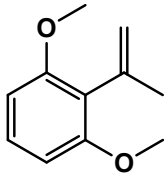
a) alkylating 2,6-dihydroxyacetophenone or a pharmaceutically acceptable salt, thereof, to form a compound of Formula 2



2

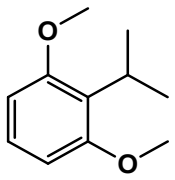
or a pharmaceutically acceptable salt thereof;

b) treating the compound of Formula 2 or a pharmaceutically acceptable salt thereof with a Grignard reagent, followed by elimination of water under acidic conditions to form a compound of Formula 3



or a pharmaceutically acceptable salt thereof;

c) hydrogenating the compound of Formula 3 or a pharmaceutically acceptable salt thereof to form a compound of Formula 4



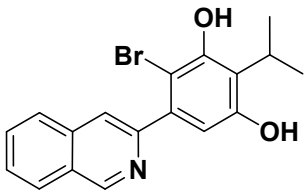
4

or a pharmaceutically acceptable salt thereof; and

d) borylating the compound of Formula 4 or a pharmaceutically acceptable salt thereof to form the compound of Formula 5 or a pharmaceutically acceptable salt thereof.

28. The process of claim 25 wherein the demethylation comprises

a) treating the compound of Formula 7 with boron tribromide to form the compound of Formula 7-1



7-1

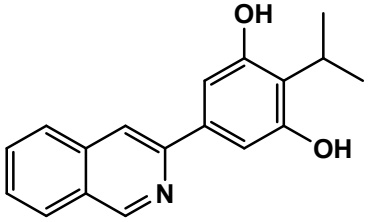
and

b) hydrogenating the compound of Formula 7-1 to form the compound of Formula 8.

29. The process of claim 25, further comprising purifying the compound of Formula 8.

30. The process of claim 29 wherein the purifying comprises crystallization

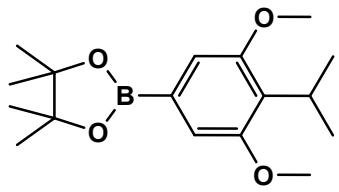
31. A process for preparing a compound of Formula 8



8

or a pharmaceutically acceptable salt, solvate or hydrate thereof, comprising:

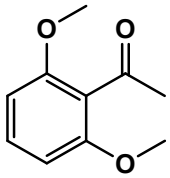
a) preparing a compound of Formula 5



5

or a pharmaceutically acceptable salt, solvate or hydrate thereof, comprising

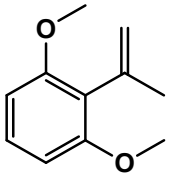
1) alkylating 2,6-dihydroxyacetophenone or a pharmaceutically acceptable salt, solvate or hydrate thereof, to form a compound of Formula 2



2

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

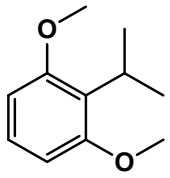
2) treating the ketone of Formula 2 or a pharmaceutically acceptable salt, solvate or hydrate thereof with a Grignard reagent, followed by elimination of water under acidic conditions to form a compound of Formula 3



3

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

3) hydrogenating the compound of Formula 3 or a pharmaceutically acceptable salt, solvate or hydrate thereof to form a compound of Formula 4



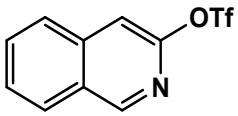
4

or a pharmaceutically acceptable salt, solvate or hydrate thereof; and

4) borylating the compound of Formula 4 or a pharmaceutically acceptable salt, solvate or hydrate thereof to form the compound of Formula 5

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

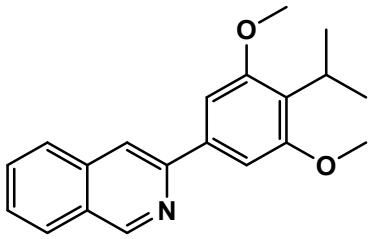
b) preparing a compound of Formula 6



6

or a pharmaceutically acceptable salt, solvate or hydrate thereof comprising treating isoquinoline-3-ol with a triflating agent; and

c) coupling the compound of Formula 6 or a pharmaceutically acceptable salt, solvate or hydrate thereof with the compound of Formula 5 or a pharmaceutically acceptable salt, solvate or hydrate thereof to form a compound of Formula 7



7

or a pharmaceutically acceptable salt, solvate or hydrate thereof; and

d) demethylating the compound of Formula 7 to form the compound of Formula 8.

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein steps a and b can be done in either order or simultaneously in different reaction vessels.

32. The process according to claim 31, further comprising purifying the compound of Formula 8.

33. The process according to claim 31 wherein the purifying comprises crystallization.

34. The compound according to any one of claims 1 to 13, or the pharmaceutical composition according to any one of claims 14 to 16, for use as a medicament.