I,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

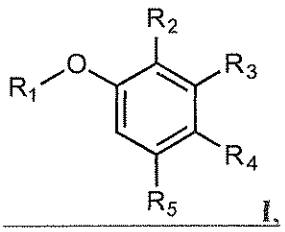
R_2 is nitro, carboxaldehyde, carboxylic acid, ester, amido, cyano, halo, sulfonyl, alkyl or heteroalkyl;

R_3 is hydrogen, halo, cyano, alkyl, heteroalkyl, alkenyl, alkynyl, alkylamino, carboxaldehyde, carboxylic acid, oxime, ester, amido or acyl, or R_2/R_3 and atoms they are attached to form a 5- or 6- membered carbocycle with at least one sp^3 hybridized carbon;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; and

R_5 is hydrogen, halo or alkyl.

[006a] In another aspect, the present disclosure provides a compound represented by Formula I:



I,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

R_2 is nitro, carboxaldehyde, carboxylic acid, ester, amido, cyano, halo, sulfonyl or alkyl;

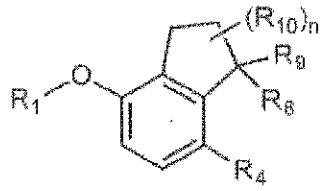
R_3 is hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, alkylamino, carboxaldehyde, carboxylic acid, ester, oxime, amido or acyl; or R_2/R_3 and atoms they are attached to form a 5- or 6-membered carbocycle with at least one sp^3 hybridized carbon;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; and

R_5 is hydrogen, halo or alkyl;

with the proviso that when R_3 is hydrogen, R_4 is $-S(=O)_2R_a$ or $-S(=O)(=NR_b)R_c$, wherein R_a is fluoroalkyl, R_b is hydrogen, cyano or alkyl, and R_c is alkyl.

[006b] In another aspect, the present disclosure provides a compound represented by Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, 2, 3 or 4;

R_1 is monocyclic aryl or monocyclic heteroaryl;

R_8 is hydrogen, hydroxy, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl, or R_8 and R_9 in combination form oxo; and

each of R_{10} is independently selected from the group consisting of fluoro, hydroxy, alkyl, and heteroalkyl, with the proviso that when R_{10} is hydroxy, n is 1 or 2.

[007] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier or excipient. The compound may exist in an amorphous form, a crystalline form, or as a salt, solvate or hydrate.

[008] In another aspect, the present disclosure provides a method of treating renal cell carcinoma by administrating a therapeutically effective amount of a compound described herein or a pharmaceutical composition thereof to a subject in need of such treatment. In some embodiments, the subject is a human.

[008a] In another aspect, there is provided use of a therapeutically effective amount of a compound as described herein in the manufacture of a medicament for treating renal cell carcinoma (RCC) in a subject.

[009] In another aspect, the present disclosure provides a method of inhibiting the activities of HIF-2α in a cell, comprising contacting the cell with an effective amount of a compound described herein.

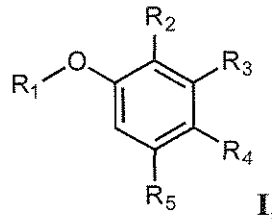
[010] In another aspect, the present disclosure provides a kit comprising a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier or excipient and an instruction for using the composition to treat a subject suffering from cancer. In some embodiments, the cancer is renal cell carcinoma.

Brief Description of Figures

[011] **Figure 1** shows treatment of renal cell carcinoma 786-O xenograft bearing mice at 0 mg/kg (denoted as "Veh"), 10 mg/kg, 30 mg/kg, and 100 mg/kg of **Compound 15** three times each at 12 hour intervals. **Figure 1** shows that **Compound 15** treatment of renal cell carcinoma 786-O xenograft bearing mice reduced the mRNA levels of HIF-2α and HIF-2α-regulated genes (PAI-1, CCND1, VEGFA, and GLUT1) in tumor. **Compound 15** had no

What is claimed is:

1. A compound represented by Formula I:



I,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

R_2 is nitro, carboxaldehyde, carboxylic acid, ester, amido, cyano, halo, sulfonyl or alkyl;

R_3 is hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, alkylamino, carboxaldehyde, carboxylic acid, ester, oxime, amido or acyl; or R_2/R_3 and atoms they are attached to form a 5- or 6-membered carbocycle with at least one sp^3 hybridized carbon;

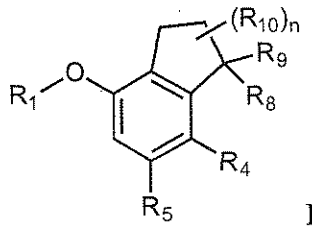
R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; and

R_5 is hydrogen, halo or alkyl;

with the proviso that when R_3 is hydrogen, R_4 is $-S(=O)_2R_a$ or $-S(=O)(=NR_b)R_c$, wherein R_a is fluoroalkyl, R_b is hydrogen, cyano or alkyl, and R_c is alkyl.

2. The compound of claim 1, wherein R_2/R_3 and atoms they are attached to form a 5- or 6-membered carbocycle with at least one sp^3 hybridized carbon, wherein said carbocycle is substituted with fluoro, chloro, hydroxy, alkyl or heteroalkyl.

3. The compound of claim 1, represented by Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, 3 or 4;

R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

each of R_{10} is independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl.

4. The compound of claim 3, wherein R_1 is phenyl or pyridyl, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

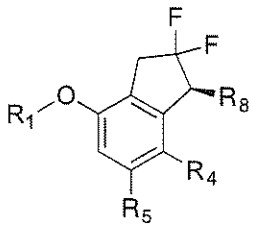
5. The compound of claim 3, wherein R_8 is hydroxy or amino.

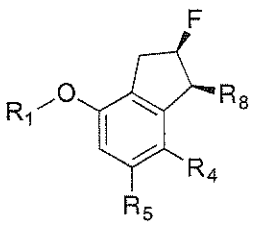
6. The compound of claim 3, wherein R_9 is hydrogen.

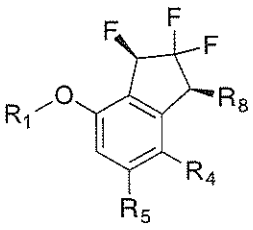
7. The compound of claim 3, wherein R_{10} is fluoro and n is 1, 2 or 3.

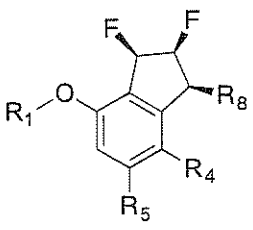
8. The compound of claim 3, wherein R_4 is cyano, fluoroalkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; R_5 is hydrogen; R_8 is hydroxy or amino; and R_9 is hydrogen.

9. The compound of claim 1, represented by Formula Va, Vb, Vc, or Vd:


Va


Vb


Vc


Vd

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is aryl or heteroaryl;

R_4 is halo, cyano, alkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl;

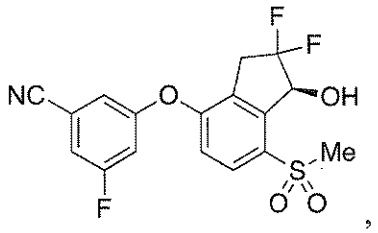
R_5 is hydrogen, halo or alkyl; and

R_8 is hydroxy, alkylamino, alkoxy or amino.

10. The compound of claim 9, wherein R_1 is phenyl or pyridyl, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

11. The compound of claim 9, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl; R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl; R_5 is hydrogen; and R_8 is hydroxy or amino.

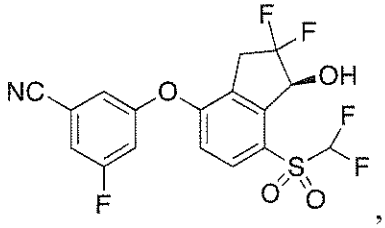
12. The compound of claim 1, wherein the compound is (*S*)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile, represented by the formula:



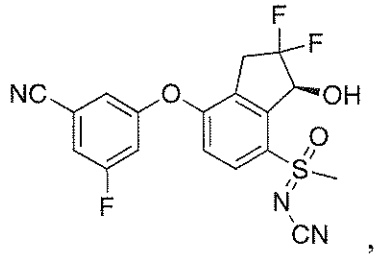
or a pharmaceutically acceptable salt thereof.

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

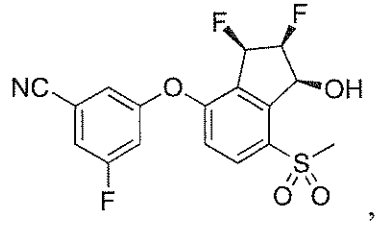
(a) 3-[(1*S*)-7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:



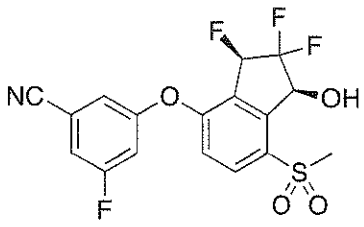
(b) *N*-(((*S*)-7-(3-cyano-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydro-1*H*-inden-4-yl)(methyl)(oxo)-λ^6-sulfanylidene)cyanamide, represented by the formula:



(c) 3-[(1*S*,2*S*,3*R*)-2,3-difluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-5-fluoro-benzonitrile, represented by the formula:

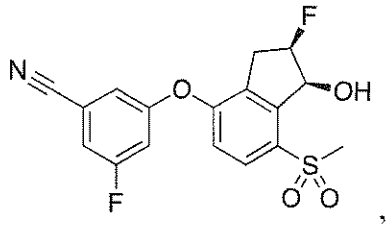


(d) 3-fluoro-5-[(1*S*,3*R*)-2,2,3-trifluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-benzonitrile, represented by the formula:



, and

(e) 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile, represented by the formula:



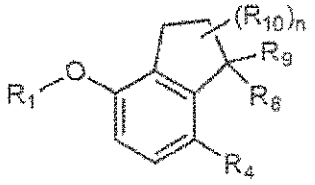
,

or a pharmaceutical acceptable salt of any one thereof.

14. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. Use of a therapeutically effective amount of a compound of claim 1 in the manufacture of a medicament for treating renal cell carcinoma (RCC) in a subject.

16. A compound represented by Formula III:



III

,

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, 2, 3 or 4;

R_1 is monocyclic aryl or monocyclic heteroaryl;

R_8 is hydrogen, hydroxy, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl, or R_8 and R_9 in combination form oxo; and

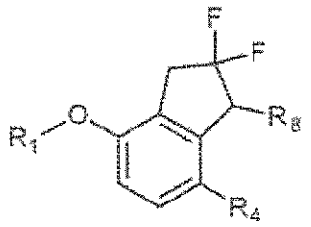
each of R_{10} is independently selected from the group consisting of fluoro, hydroxy, alkyl, and heteroalkyl, with the proviso that when R_{10} is hydroxy, n is 1 or 2.

17. The compound of claim 16, wherein R_8 is hydroxy or amino.

18. The compound of claim 16, wherein R_9 is hydrogen.

19. The compound of claim 16, wherein n is 1 or 2 and R_{10} is fluoro.

20. The compound of claim 16, represented by Formula IV:



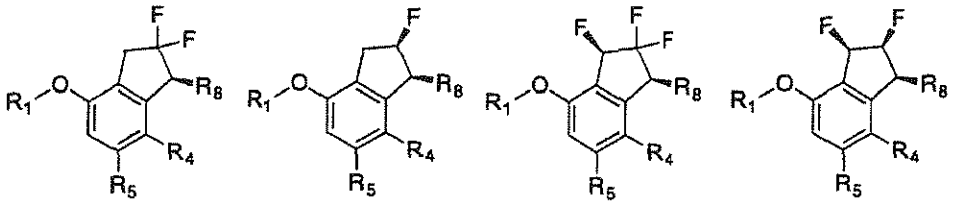
IV

,

or a pharmaceutically acceptable salt thereof, wherein R_8 is hydroxy or amino.

What is claimed is:

1. A compound having one of the formulae:



Va Vb Vc Vd

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl or heteroaryl;

R_4 is halo, cyano, alkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl; and

R_8 is hydroxy, alkylamino, alkoxy or amino.

2. The compound of claim 1, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl.

3. The compound of claim 2, wherein R_1 is phenyl or pyridyl.

4. The compound of claim 3, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

5. The compound of claim 2, wherein R_1 is pyridyl N-oxide.

6. The compound of claim 5, wherein said pyridyl N-oxide is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

7. The compound of claim 1, wherein R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl.

8. The compound of claim 7, wherein R_4 is selected from the group consisting of —CN, —CF_3, —S(=O)CH_3, —$S(=O)_2CH_3$, —$S(=O)_2CH_2F$, —$S(=O)_2CHF_2$, —$S(=O)_2CF_3$, —$S(=O)_2NH_2$, —$S(=O)_2NHCH_3$, —S(=O)(=NH)CH_3, —S(=O)(=NH)CH_2F, —S(=O)(=NH)CHF_2, —S(=O)(=NH)CF_3, —S(=O)(=N-CN)CH_3, —S(=O)(=N-CN)CH_2F, —S(=O)(=N-CN)CHF_2, and —S(=O)(=N-CN)CF_3.

9. The compound of claim 1, wherein R_5 is hydrogen.

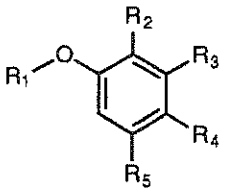
10. The compound of claim 1, wherein R_8 is hydroxy or amino.

11. The compound of claim 10, wherein R_8 is hydroxy.

12. The compound of claim 1, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl; R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl; R_5 is hydrogen; and R_8 is hydroxy or amino.

13. The compound of claim 1 or 12, wherein enantiomeric excess of said compound is at least about 80%.

14. A compound of Formula I



I,

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl or heteroaryl;

R_2 is nitro, carboxaldehyde, carboxylic acid, ester, amido, cyano, halo, sulfonyl or alkyl;

R_3 is hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, alkylamino, carboxaldehyde, carboxylic acid, ester, oxime, amido or acyl; or R_2/R_3 and atoms they are attached to form a 5- or 6-membered carbocycle with at least one sp^3 hybridized carbon;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; and

R_5 is hydrogen, halo or alkyl;

with the proviso that when R_3 is hydrogen, R_4 is $-S(=O)_2R_a$ or $-S(=O)(=NR_b)R_c$, wherein R_a is fluoroalkyl, R_b is hydrogen, cyano or alkyl, and R_c is alkyl.

15. The compound of claim 14, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl.

16. The compound of claim 15, wherein R_1 is phenyl or pyridyl.

17. The compound of claim 16, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

18. The compound of claim 15, wherein R_1 is pyridyl N-oxide.

19. The compound of claim 18, wherein said pyridyl N-oxide is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

20. The compound of claim 14, wherein R_2 is halo, cyano or alkyl.

21. The compound of claim 14, wherein R_3 is halo, cyano or alkyl.

22. The compound of claim 21, wherein R_3 is $-(CH_2)_nOH$, and wherein n is 1, 2 or 3.

23. The compound of claim 22, wherein n is 1.

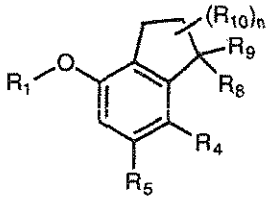
24. The compound of claim 14, wherein R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl.

25. The compound of claim 14, wherein R_5 is hydrogen.

26. The compound of claim 15, wherein R_2 is halo, cyano or alkyl; R_3 is halo, cyano or alkyl; R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl; and R_5 is hydrogen.

27. The compound of claim 26, wherein R_3 is $-CH_2OH$.

28. A compound of Formula III



III,

or a pharmaceutically acceptable salt thereof,

wherein:

n is 1, 2, 3 or 4;

R_1 is aryl or heteroaryl;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen, halo or alkyl;

R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino;

R_9 is hydrogen, alkyl, alkenyl or alkynyl; or R_8 and R_9 in combination form oxo or oxime; and

each of R_{10} is independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxy, and alkyl; or two R_{10} and the carbon atom(s) they are attached to form a 3- to 8-membered cycloalkyl or heterocycloalkyl.

29. The compound of claim 28, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl.

30. The compound of claim 29, wherein R_1 is phenyl or pyridyl.

31. The compound of claim 30, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

32. The compound of claim 29, wherein R_1 is pyridyl N-oxide.

33. The compound of claim 32, wherein said pyridyl N-oxide is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

34. The compound of claim 28, wherein R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl.

35. The compound of claim 28, wherein R_5 is hydrogen.

36. The compound of claim 28, wherein R_8 is hydroxy or amino.

37. The compound of claim 36, wherein R_8 is hydroxy.

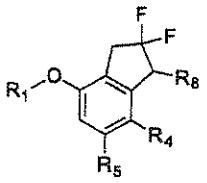
38. The compound of claim 28, wherein R_9 is hydrogen.

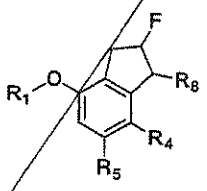
39. The compound of claim 28, wherein R_{10} is fluoro and n is 1, 2 or 3.

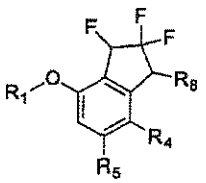
40. The compound of claim 29, wherein R_4 is cyano, fluoroalkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl; R_5 is hydrogen; R_8 is hydroxy or amino; and R_9 is hydrogen.

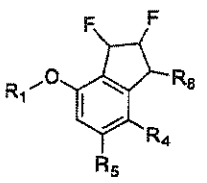
41. The compound of claim 40, wherein R_{10} is fluoro.

42. A compound having one of the formulae:


IVa


IVb


IVc


IVd

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl or heteroaryl;

R_4 is nitro, halo, cyano, alkyl, sulfinyl, sulfonamide, sulfonyl or sulfoximinyl;

R_5 is hydrogen; halo or alkyl; and

R_8 is hydrogen, hydroxy, alkylamino, alkoxy or amino.

43. The compound of claim 42, wherein R_1 is phenyl, monocyclic heteroaryl, or bicyclic heteroaryl.

44. The compound of claim 43, wherein R_1 is phenyl or pyridyl.

45. The compound of claim 44, wherein said phenyl or pyridyl is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

46. The compound of claim 43, wherein R_1 is pyridyl N-oxide.

47. The compound of claim 46, wherein said pyridyl N-oxide is substituted with at least one substituent selected from the group consisting of halo, C1-C4 alkyl, C1-C4 alkoxy, and cyano.

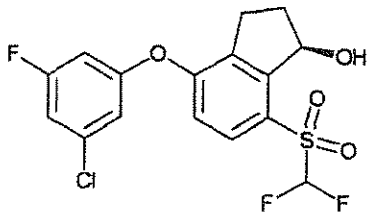
48. The compound of claim 42, wherein R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl.

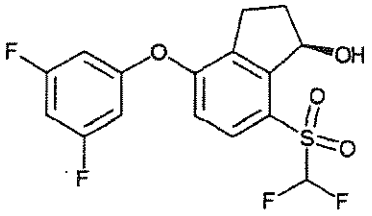
49. The compound of claim 42, wherein R_5 is hydrogen.

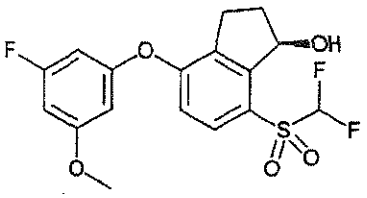
50. The compound of claim 42, wherein R_8 is amino or hydroxy.

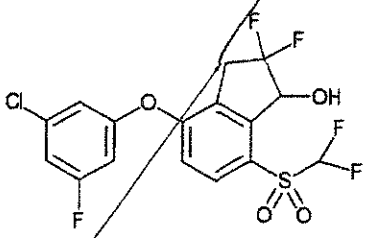
51. The compound of claim 43, wherein R_4 is cyano, fluoroalkyl, sulfonamide, sulfinyl, sulfonyl or sulfoximinyl; R_5 is hydrogen; and R_8 is amino or hydroxy.

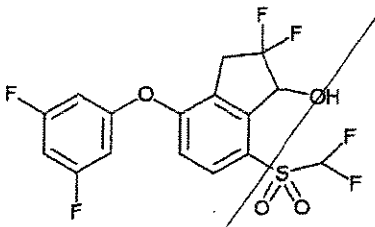
52. A compound or pharmaceutically acceptable salt selected from the group consisting of:

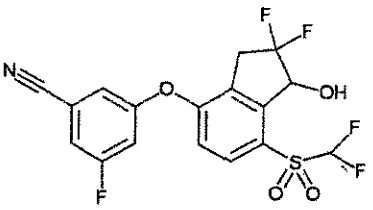


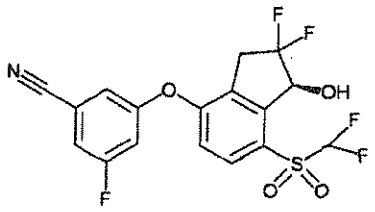


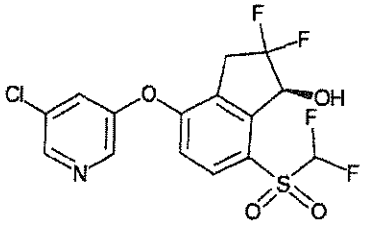


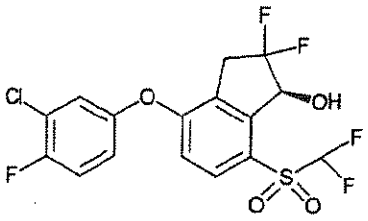


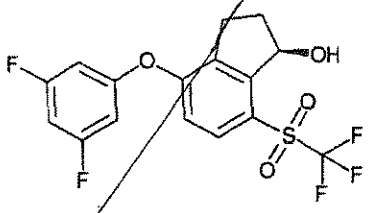


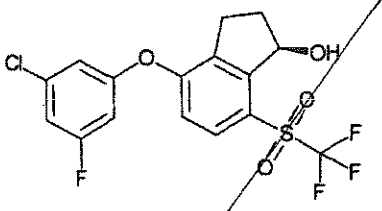


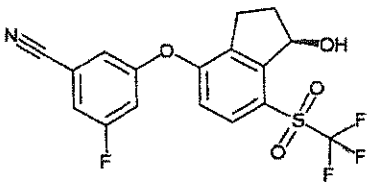


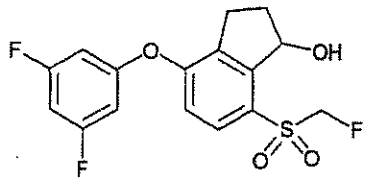


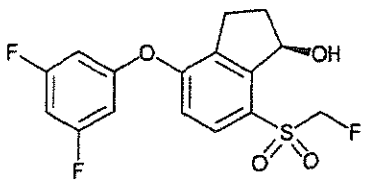


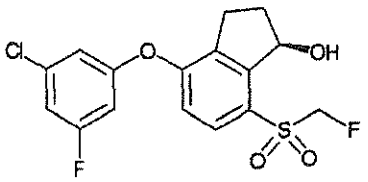


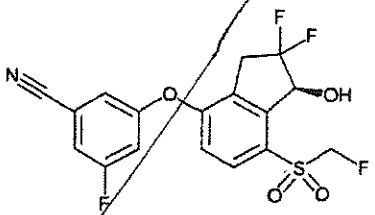


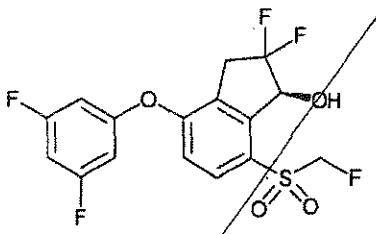


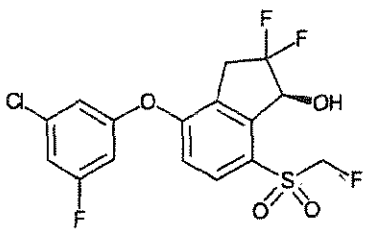


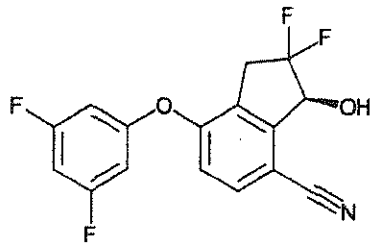


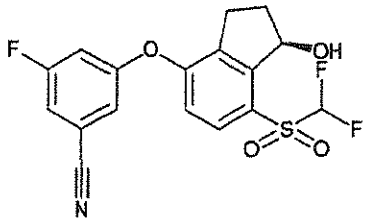


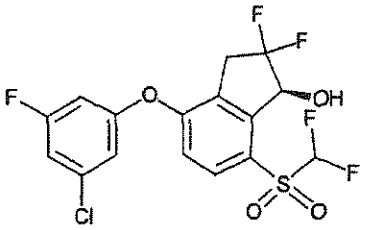


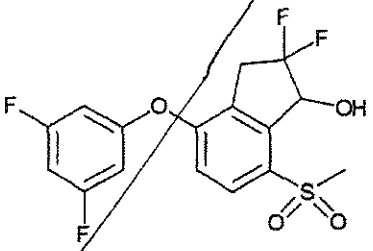


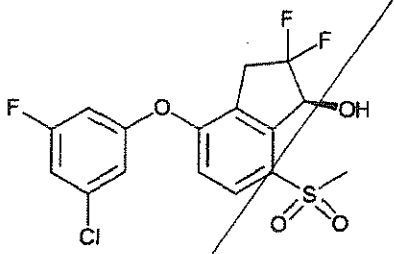


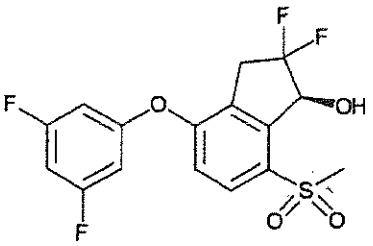


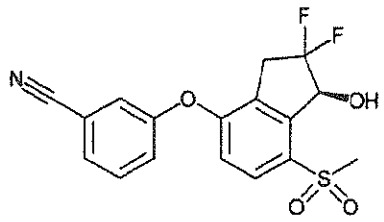


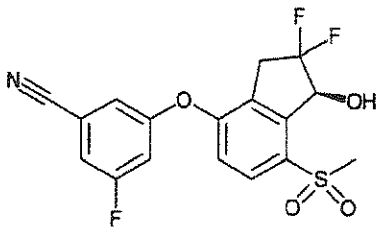


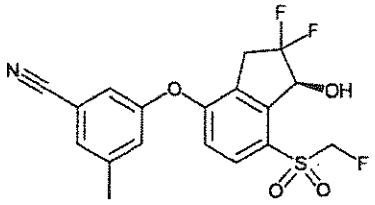


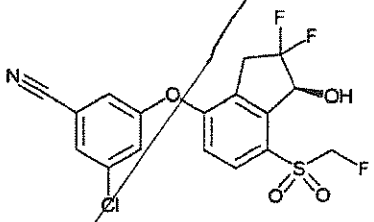


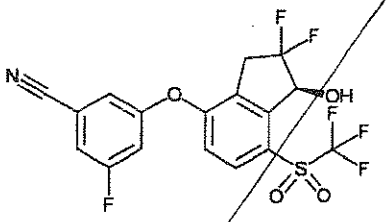


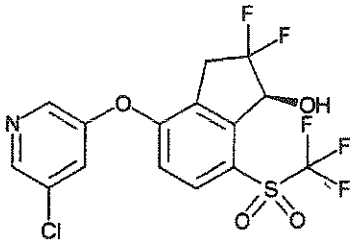


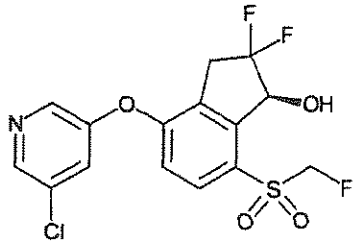


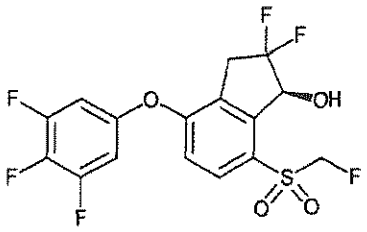


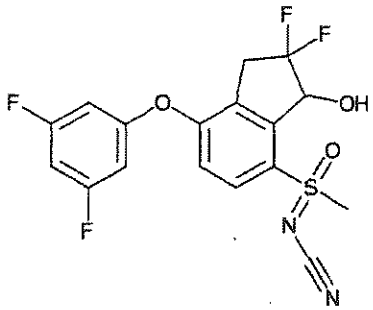


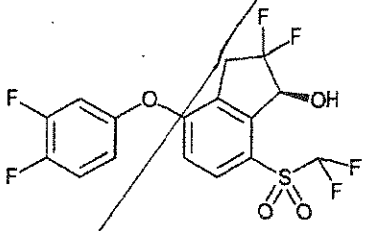


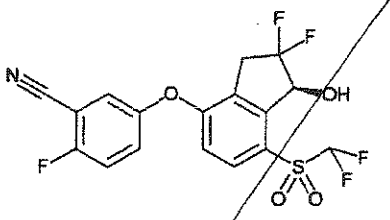


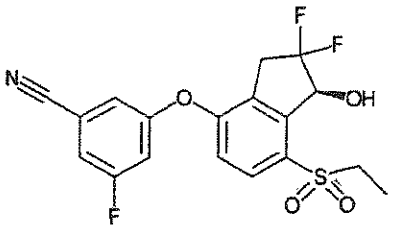


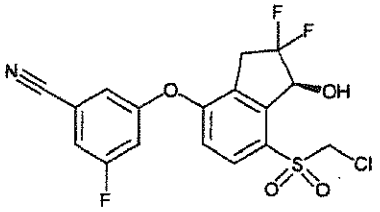


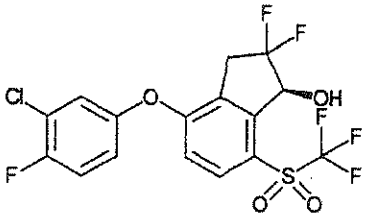


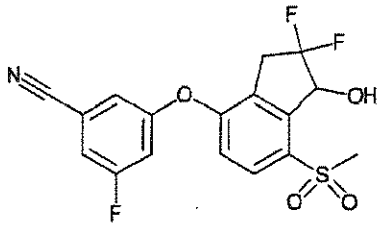


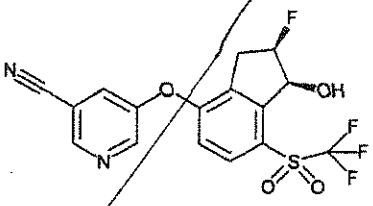


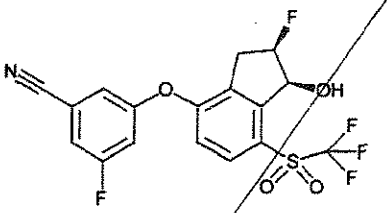


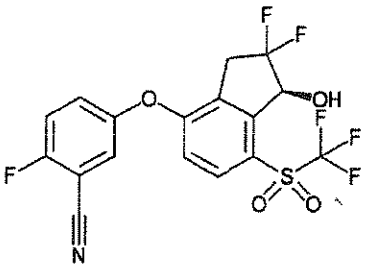


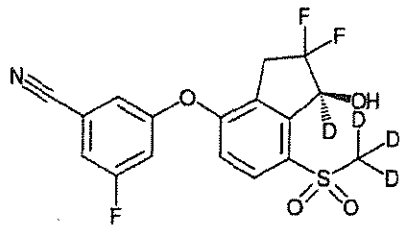


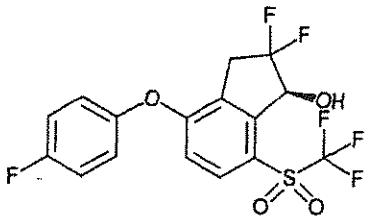


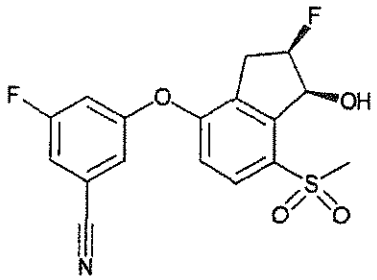


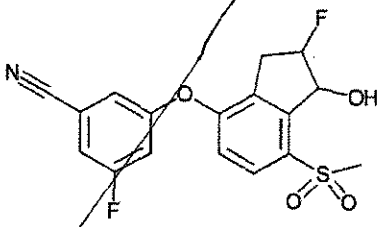


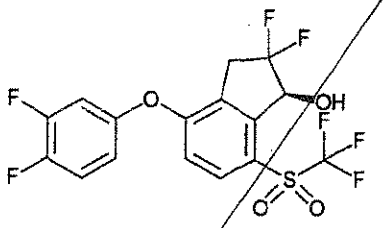


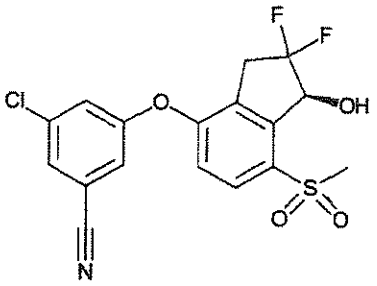


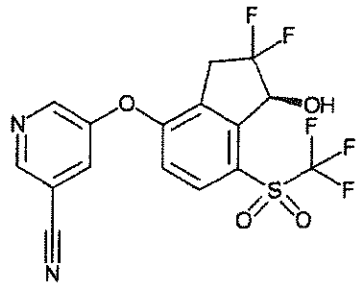


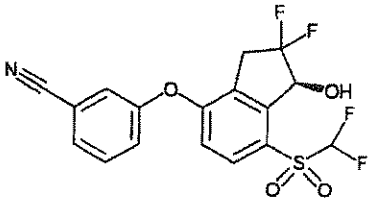


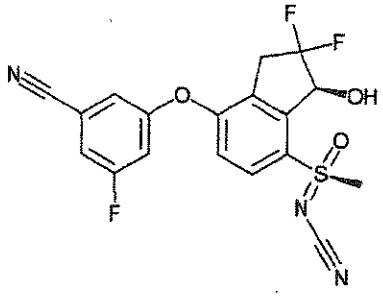


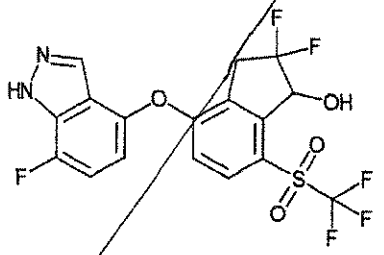


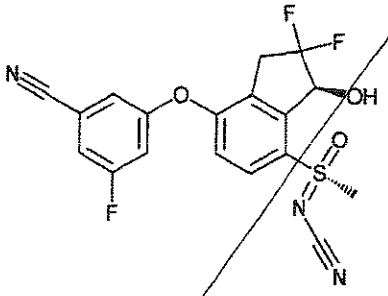


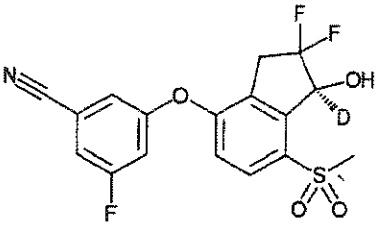


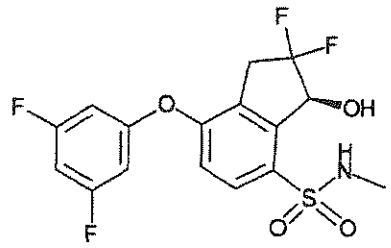


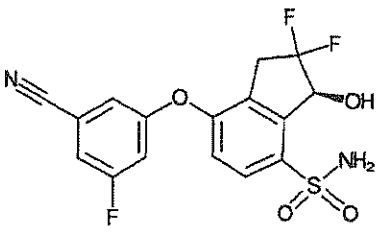


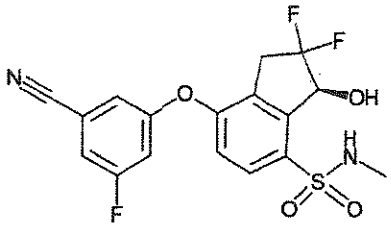


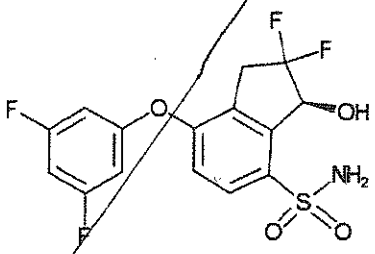


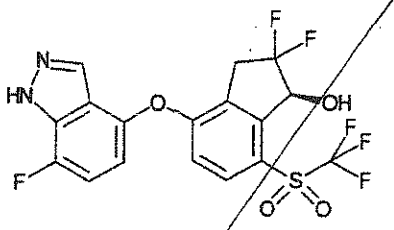


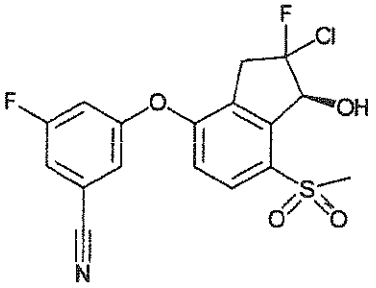


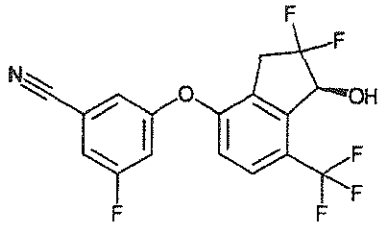


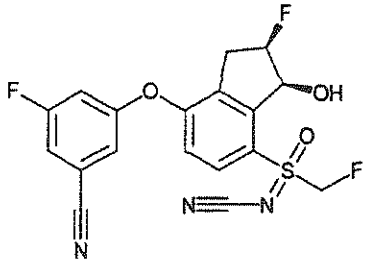


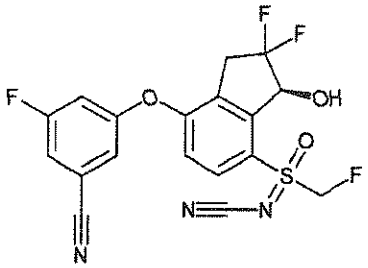


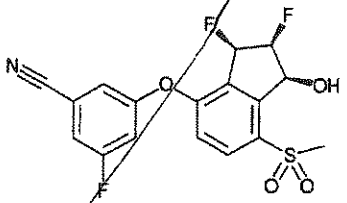


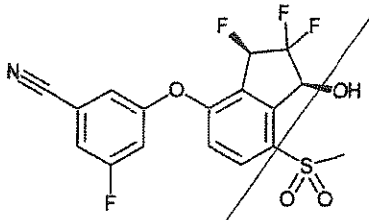


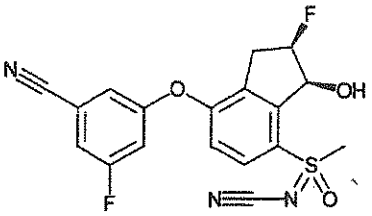


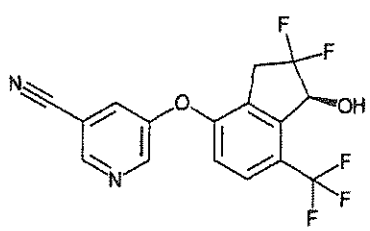


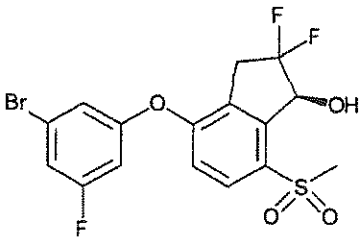


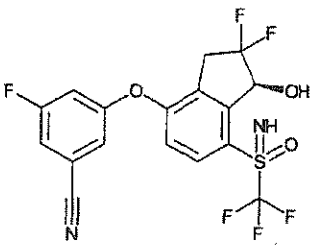


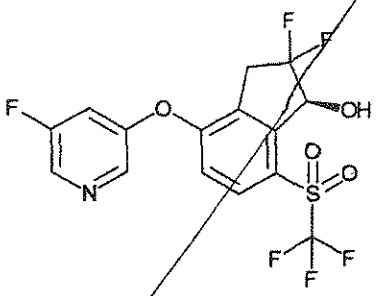


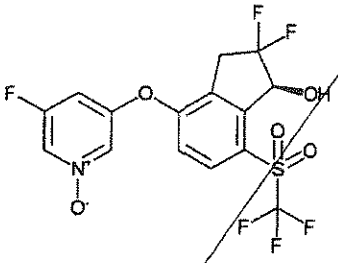


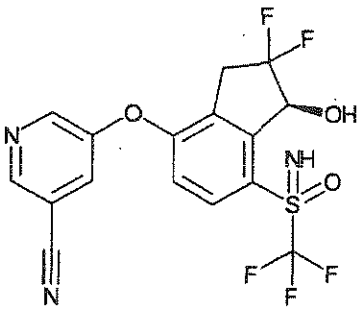


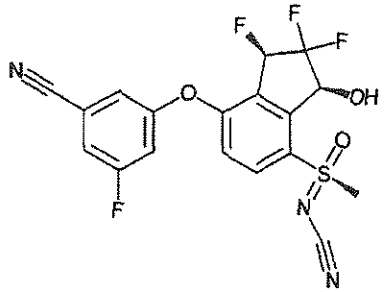


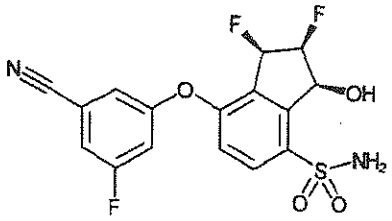


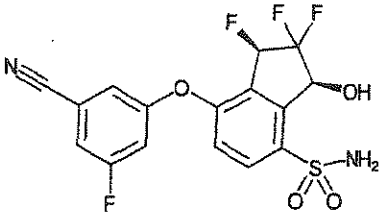


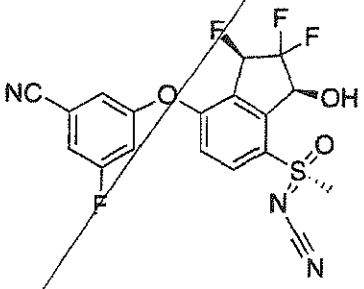




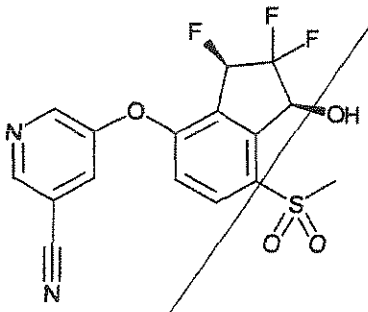








,and



53. A compound that is 3-[(1*S*)-7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-indan-4-yl]oxy-5-fluoro-benzonitrile.

54. A compound that is (*S*)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile.

55. A compound that is *N*-(((*S*)-7-(3-cyano-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydro-1*H*-inden-4-yl)(methyl)(oxo)-λ^6-sulfanylidene)cyanamide.

56. A compound that is 3-[(1*S*,2*S*,3*R*)-2,3-difluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-5-fluoro-benzonitrile.

57. A compound that is 3-fluoro-5-[(1*S*,3*R*)-2,2,3-trifluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-benzonitrile.

58. A compound that is 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile.

59. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1, 14 and 28 and a pharmaceutically acceptable carrier.

60. A method of inhibiting HIF-2α activity in a cell, comprising administering to said cell a compound of any one of claims 1, 14 and 28.

61. A method of treating renal cell carcinoma (RCC) in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to claim 59.

62. The method of claim 61, wherein said subject is a human.

63. The method of claim 61, wherein said renal cell carcinoma is clear cell renal cell carcinoma (ccRCC).

64. A kit comprising a pharmaceutical composition of claim 59 and an instruction for using the composition to treat a subject suffering from renal cell carcinoma.