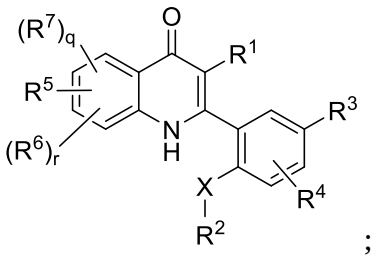
[0004] The need exists to develop effective PPARG modulators for treating cancers such as NMIUC, MIUC, and MUC, and related conditions.

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a compound having the Formula **I**:



;

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, halo, (C_1-C_4)alkyl, or hydroxyl;

X is S, SO, SO_2, or -SONH;

R^2 is (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or halo(C_1-C_4)alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or hydroxyl;

R^5 is halo, halo(C_1-C_4)alkyl, or cyano;

R^6 is halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, or cyano;

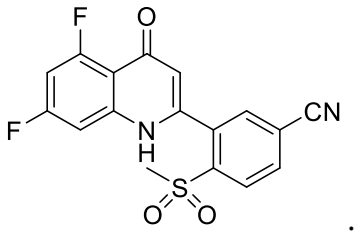
R^7 is halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, -(C_1-C_4)alkylOR^a, -(C_1-C_4)alkyl$C(O)R^a$, -(C_1-C_4)alkyl$C(O)OR^a$, $-C(O)NR^aR^b$, -(C_1-C_4)alkyl$C(O)NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, -(C_1-C_4)alkylNR^aR^b, $-C(O)NR^aSO_3H$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(S)OR^b$, $-NR^cC(O)N^aR^b$, $-NR^cC(S)NR^aR^b$, $-NR^cS(O)_2NR^aR^b$, $-C(S)R^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-C(S)OR^a$, $-C(S)NR^aR^b$, $-NR^aC(S)R^b$, $-SR^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8;

R^8 is selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, nitro, oxo, cyano, -(C_1-C_4)alkylOR^d, -(C_1-C_4)alkyl$C(O)R^d$, -(C_1-C_4)alkyl$C(O)OR^d$, $-C(O)NR^dR^e$, -(C_1-C_4)alkyl$C(O)NR^dR^e$, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, -(C_1-C_4)alkylNR^dR^e, $-C(O)NR^dSO_3H$, $-NR^dC(O)R^e$, $-NR^dC(O)OR^e$, $-NR^dC(S)OR^e$, $-NR^fC(O)N^dR^e$, $-NR^fC(S)NR^dR^e$, $-NR^fS(O)_2NR^dR^e$, $-C(S)R^d$, $-S(O)_2R^d$, $-S(O)R^d$, $-C(S)OR^d$, $-C(S)NR^dR^e$, $-NR^dC(S)R^e$, and $–SR^d$;

R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen or (C_1-C_4)alkyl; and

q and r are each independently 0 or 1.

[0004b] In another aspect of the present disclosure, there is provided a crystalline Form A of a compound of the structural formula:



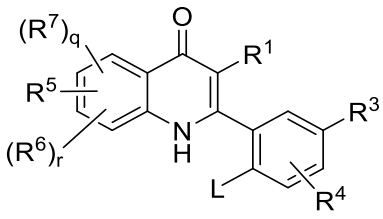
.

[0004c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the crystalline form as disclosed herein; and a pharmaceutically acceptable carrier.

[0004d] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the crystalline form as disclosed herein, in the manufacture of a medicament for treating a cancer responsive to the suppression of PPARG in a subject.

[0004e] In another aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **I** as disclosed herein, said process comprising:

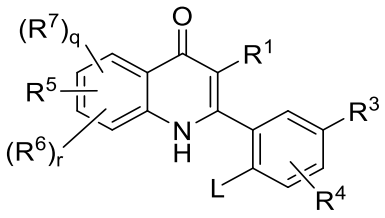
reacting a compound of Formula **A**:



(**A**),

wherein L is a leaving group, with the corresponding sulfur nucleophile of XR^2 to form the compound of Formula **I**.

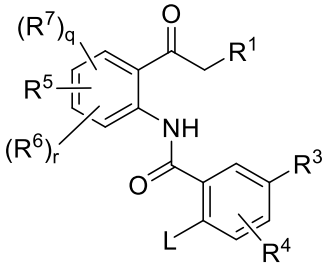
[0004f] In yet another aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **A**:



(**A**),

wherein L is a leaving group and the remaining variables are as described above for Formula **I** as disclosed herein, said process comprising:

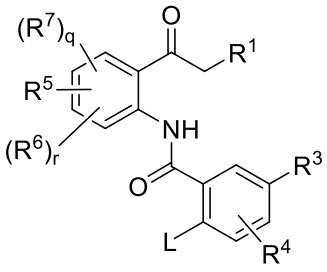
reacting a compound having the Formula **B**:



(**B**),

with a base.

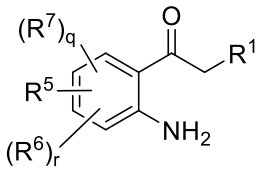
[0004g] In a further aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **B**:



(**B**),

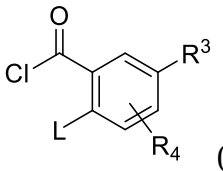
wherein L is a leaving group and the remaining variables are as described above for Formula **I** as disclosed herein, said process comprising:

reacting a compound having the Formula **C**:

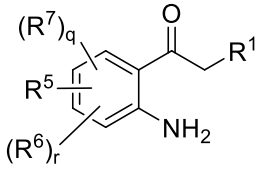


(**C**),

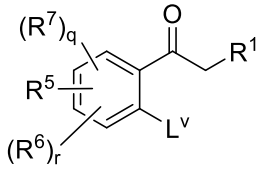
with a compound having the Formula **D**:


(**D**).

[0004h] In another aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **C**:

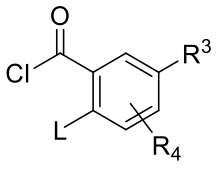

(**C**),

wherein the variables are as described above for Formula **I** as disclosed herein, said process comprising reacting a compound having the Formula **E**:

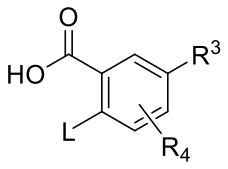

(**E**),

where L^v is a leaving group, with ammonia ion to form the compound having the Formula **C**.

[0004i] In yet another aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **D**:

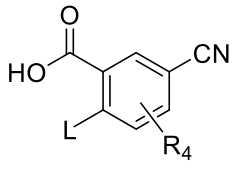

(**D**),

wherein L is a leaving group and the remaining variables are as described above for Formula **I** as disclosed herein, said process comprising reacting a compound having the Formula **F**:


(**F**),

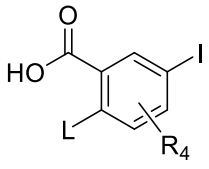
with a chlorinating agent.

[0004j] In a further aspect of the present disclosure, there is provided a process for preparing a compound having the Formula **G**:



(**G**),

wherein L is a leaving group and R^4 is as described above for Formula **I** as disclosed herein, said process comprising reacting a compound having the Formula **H**:

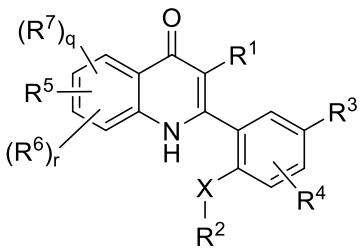


(**H**),

with a palladium catalyst.

[0004k] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the crystalline form as disclosed herein, for use in therapy.

[0005] Provided herein are compounds having the Formula **I**:



(**I**);

and pharmaceutically acceptable salts and compositions thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, q and r are as described herein. In one example, the disclosed compounds of Formula **I** and pharmaceutically acceptable salts thereof modulate PPARG (e.g., as agonists such as inverse agonists, and are useful in a variety of therapeutic applications such as, for example, in treating cancer. As such, their uses for treating diseases responsive to the inhibition of PPARG are included.

[0006] Pharmaceutical compositions comprising the compounds and pharmaceutically acceptable salts of the disclosed compounds of Formula **I**, as well as methods for their preparation are also included.

BRIEF DESCRIPTION OF THE FIGURES

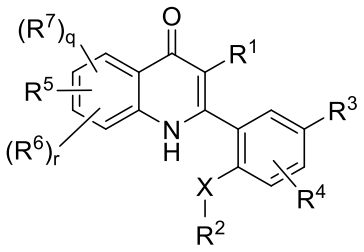
[0007] **FIG. 1** depicts an X-ray powder diffraction pattern (XRPD) for crystalline Form A of 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile.

[0008] **FIG. 2** depicts a differential scanning calorimetry (DSC) thermogram for Form A of 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile.

DETAILED DESCRIPTION

1. *General Description of Compounds*

[0009] In a first embodiment, provided herein is a compound of Formula **I**:

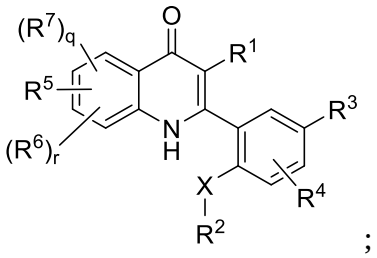


(**I**);

or a pharmaceutically acceptable salt thereof, wherein:

Listing of Claims:

1. A compound having the Formula **I**:



;

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, halo, (C_1-C_4)alkyl, or hydroxyl;

X is S, SO, SO_2, or -SONH;

R^2 is (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or halo(C_1-C_4)alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or hydroxyl;

R^5 is halo, halo(C_1-C_4)alkyl, or cyano;

R^6 is halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, or cyano;

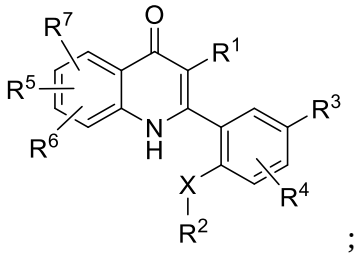
R^7 is halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, -(C_1-C_4)alkylOR^a, -(C_1-C_4)alkyl$C(O)R^a$, -(C_1-C_4)alkyl$C(O)OR^a$, $-C(O)NR^aR^b$, -(C_1-C_4)alkyl$C(O)NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, -(C_1-C_4)alkylNR^aR^b, $-C(O)NR^aSO_3H$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(S)OR^b$, $-NR^cC(O)N^aR^b$, $-NR^cC(S)NR^aR^b$, $-NR^cS(O)_2NR^aR^b$, $-C(S)R^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-C(S)OR^a$, $-C(S)NR^aR^b$, $-NR^aC(S)R^b$, $-SR^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8;

R^8 is selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, nitro, oxo, cyano, -(C_1-C_4)alkylOR^d, -(C_1-C_4)alkyl$C(O)R^d$, -(C_1-C_4)alkyl$C(O)OR^d$, $-C(O)NR^dR^e$, -(C_1-C_4)alkyl$C(O)NR^dR^e$, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, -(C_1-C_4)alkylNR^dR^e, $-C(O)NR^dSO_3H$, $-NR^dC(O)R^e$, $-NR^dC(O)OR^e$, $-NR^dC(S)OR^e$, $-NR^fC(O)N^dR^e$, $-NR^fC(S)NR^dR^e$, $-NR^fS(O)_2NR^dR^e$, $-C(S)R^d$, $-S(O)_2R^d$, $-S(O)R^d$, $-C(S)OR^d$, $-C(S)NR^dR^e$, $-NR^dC(S)R^e$, and $-SR^d$;

R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen or (C_1-C_4)alkyl; and

q and r are each independently 0 or 1.

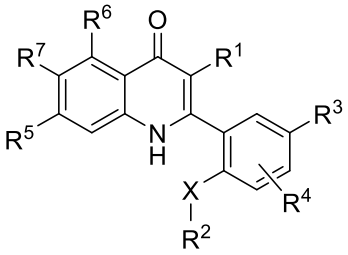
2. The compound of Claim 1, wherein the compound is of the Formula **II**:



;

or a pharmaceutically acceptable salt thereof.

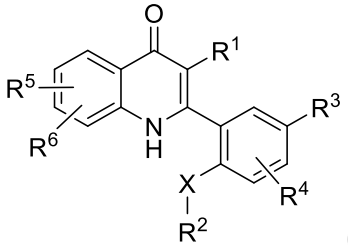
3. The compound of Claim 1 or 2, wherein the compound is of the Formula **II^{a}**:



(**II^{a}**);

or a pharmaceutically acceptable salt thereof.

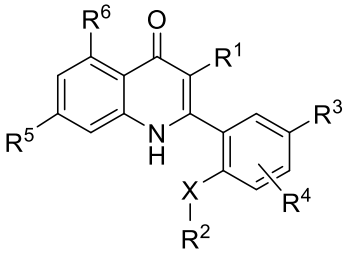
4. The compound of Claim 1, wherein the compound is of the Formula **III**:



(**III**);

or a pharmaceutically acceptable salt thereof.

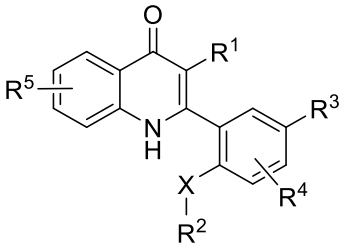
5. The compound of Claim 1 or 4, wherein the compound is of the Formula **III^{a}**:



(**III^{a}**);

or a pharmaceutically acceptable salt thereof.

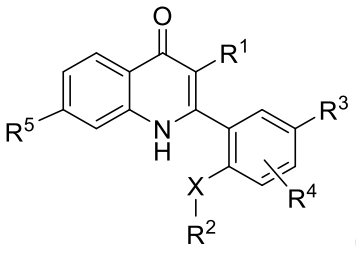
6. The compound of Claim 1, wherein the compound is of the Formula **IV**:



(**IV**);

or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 1 or 6, wherein the compound is of the Formula **IV^{a}**:



(**IV^{a}**);

or a pharmaceutically acceptable salt thereof.

8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^3 is cyano.

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^5 is halo or cyano.

11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^5 is halo.

12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^5 is chloro or fluoro.

13. The compound of any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^5 is fluoro.

14. The compound of any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^6 is halo.

15. The compound of any one of Claims 1 to 5 and 14, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro or chloro.

16. The compound of any one of Claims 1 to 5, 14, and 15, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro.

17. The compound of any one of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

18. The compound of any one of Claims 1 to 3 and 8 to 17, or a pharmaceutically acceptable salt thereof, wherein R^7 is halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylOR^a, -$C(O)NR^aR^b$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8.

19. The compound of any one of Claims 1 to 3 and 8 to 18, or a pharmaceutically acceptable salt thereof, wherein R^7 is halo, halo(C_1-C_4)alkyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylOR^a, -$C(O)NR^aR^b$, phenyl, pyridinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl, pyrazolyl, and oxetanyl, wherein each of said phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, piperidinyl, and oxetanyl are optionally and independently substituted with 1 to 3 groups selected from R^8.

20. The compound of any one of Claims 1 to 3 and 8 to 19, or a pharmaceutically acceptable salt thereof, wherein R^7 is pyrazolyl, pyridinyl, or piperazinyl, each of which optionally and independently substituted with 1 to 3 groups selected from R^8.

21. The compound of any one of Claims 1 to 3 and 8 to 20, or a pharmaceutically acceptable salt thereof, wherein R^7 is pyrazolyl optionally and independently substituted with 1 to 3 groups selected from R^8.

22. The compound of any one of Claims 1 to 3 and 8 to 21, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from halo, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, oxo, and cyano.

23. The compound of any one of Claims 1 to 3 and 8 to 22, or a pharmaceutically acceptable salt thereof, wherein R^8 is halo$(C_1$-$C_4)$alkyl.

24. The compound of any one of Claims 1 to 3 and 8 to 22, or a pharmaceutically acceptable salt thereof, wherein R^8 is $(C_1$-$C_4)$alkyl.

25. The compound of any one of Claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^2 is halo$(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkyl.

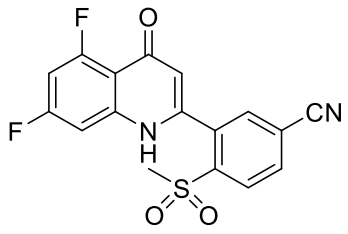
26. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^2 is CH_3, CH_2CH_3, CF_3CH_2, CF_3, $CH(CH_3)_2$, or $CH_2CH(CH_3)_2$.

27. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^2 is $(C_1$-$C_4)$alkyl.

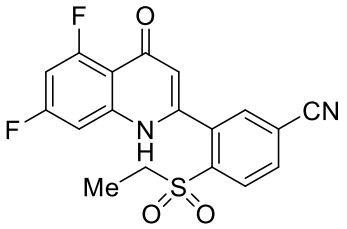
28. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^2 is CH_3.

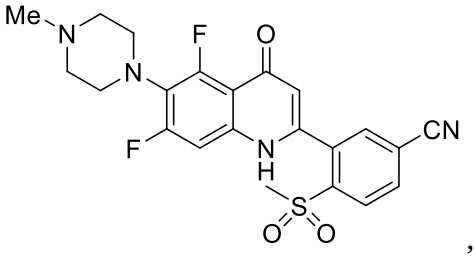
29. The compound of any one of Claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein X is SO_2.

30. The compound of Claim 1, wherein the compound is of the structural formula:



,


,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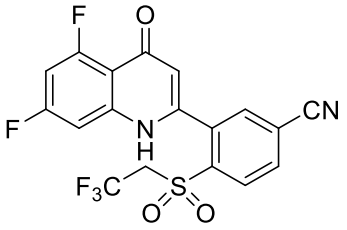
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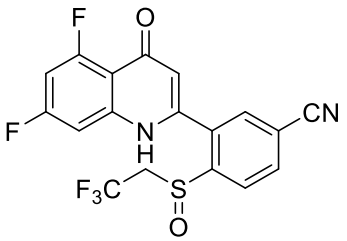
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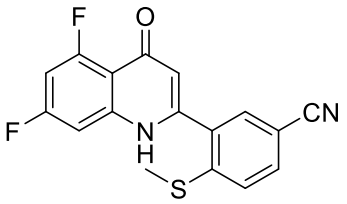
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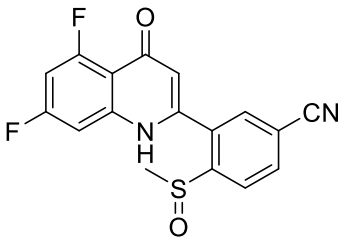
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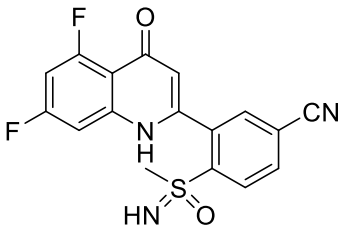
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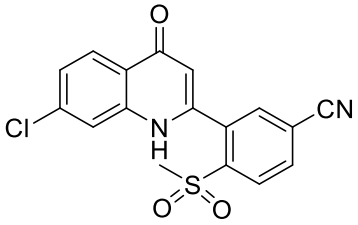
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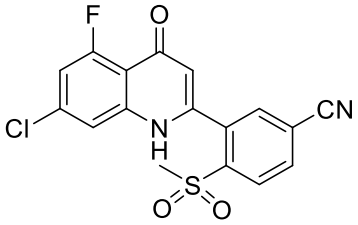
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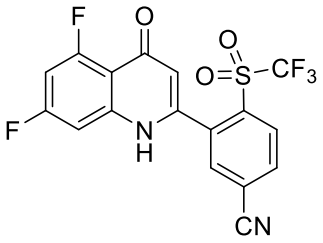
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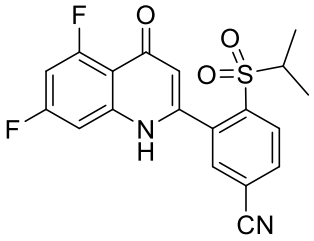
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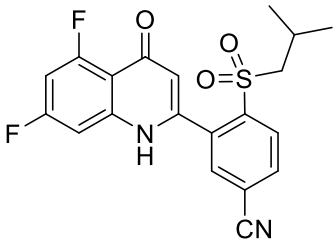
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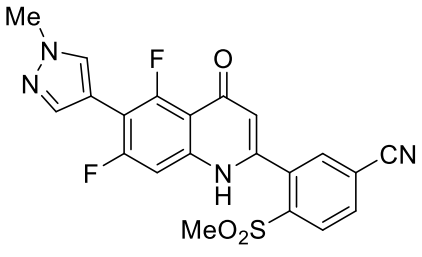
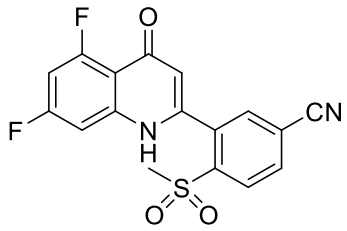

;

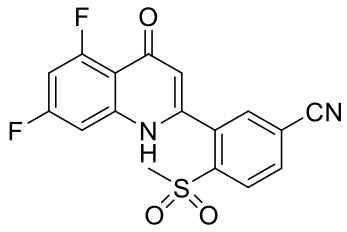
or a pharmaceutically acceptable salt of any of the foregoing.

31. The compound of Claim 1, wherein the compound is of the structural formula:



; or a pharmaceutically acceptable salt thereof.

32. Crystalline Form A of a compound of the structural formula:



.

33. The crystalline Form A of Claim 32, wherein the crystalline form is characterized by at least three x-ray powder diffraction peaks at 2Θ angles selected from 6.1º, 9.3º, 12.7º, 18.8º, and 19.8º.

34. The crystalline Form A of Claim 32 or 33, wherein the crystalline form is characterized by at least four x-ray powder diffraction peaks at 2Θ angles selected from 6.1º, 9.3º, 12.7º, 18.8º, and 19.8º.

35. The crystalline Form A of any one of Claims 32 to 34, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1º, 9.3º, 12.7º, 18.8º, and 19.8º.

36. The crystalline Form A of Claim 32 or 33, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1º, 9.3º, and 12.7º.

37. The crystalline Form A of Claim 32 or 33, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1º, 9.3º, 12.7º, and 19.8º.

38. The crystalline Form A of Claim 32 or 33, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1°, 9.3°, 12.7°, 17.7°, 18.8°, 19.8°, and 22.2°.

39. A pharmaceutical composition comprising a compound of any one of Claims 1 to 31, or a pharmaceutically acceptable salt thereof, or the crystalline form of any one of Claims 32 to 38; and a pharmaceutically acceptable carrier.

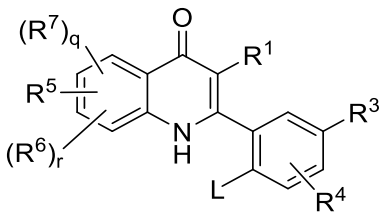
40. Use of a compound of any one of Claims 1 to 31, or a pharmaceutically acceptable salt thereof, or the crystalline form of any one of Claims 32 to 39, in the manufacture of a medicament for treating a cancer responsive to the suppression of PPARG in a subject.

41. The use of Claim 40, wherein the cancer is selected from breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, renal cancer, bladder cancer, testicular cancer, urothelial cancer, skin cancer, melanoma, colon cancer, kidney cancer, brain cancer and a hematopoietic cancer.

42. The use of Claim 40 or 41, wherein the cancer is bladder cancer.

43. A process for preparing a compound having the Formula **I** of Claim 1, said process comprising:

reacting a compound of Formula **A**:



(**A**),

wherein L is a leaving group, with the corresponding sulfur nucleophile of XR^2 to form the compound of Formula **I**.

44. The process of Claim 43, wherein the compound of Formula **A** is reacted with the sulfur nucleophile in the presence of a copper catalyst.

45. The process of Claim 44, wherein the copper catalyst is CuI.

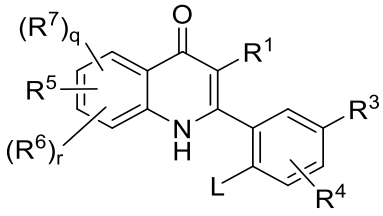
46. The process of any one of Claims 43 to 45, wherein the compound of Formula **A** is reacted with the sulfur nucleophile in the presence of a copper ligand.

47. The process of Claim 46, wherein the copper ligand is proline.

48. The process of any one of Claims 43 to 47, wherein q and r are each 0.

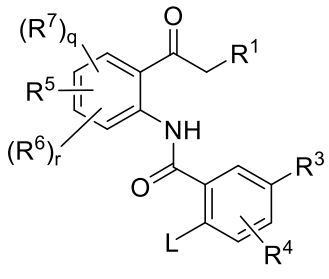
49. The process of any one of Claims 43 to 48, wherein L is chloro.

50. A process for preparing a compound having the Formula **A**:


(**A**),

wherein L is a leaving group and the remaining variables are as described above for Formula **I** in Claim 1, said process comprising:

reacting a compound having the Formula **B**:


(**B**),

with a base.

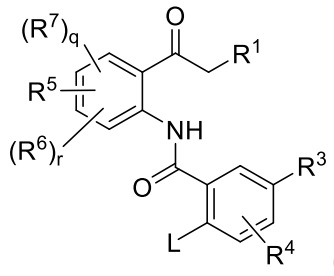
51. The process of Claim 50, wherein the base is an inorganic base.

52. The process of Claim 51, wherein the base is LiOtBu.

53. The process of any one of Claims 50 to 52, wherein q and r are each 0.

54. The process of any one of Claims 50 to 53, wherein L is chloro.

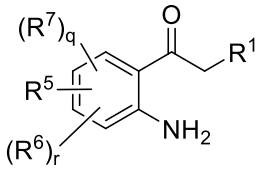
55. A process for preparing a compound having the Formula **B**:



(**B**),

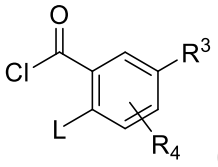
wherein L is a leaving group and the remaining variables are as described above for Formula **I** in Claim 1, said process comprising:

reacting a compound having the Formula **C**:



(**C**),

with a compound having the Formula **D**:

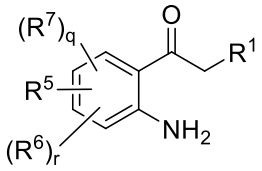


(**D**).

56. The process of Claim 55, wherein q and r are each 0.

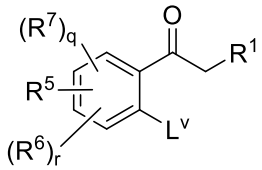
57. The process of Claim 55 or 56, wherein L is chloro.

58. A process for preparing a compound having the Formula **C**:



(**C**),

wherein the variables are as described above for Formula **I** in Claim 1, said process comprising reacting a compound having the Formula **E**:



(**E**),

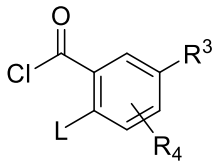
where L^v is a leaving group, with ammonia ion to form the compound having the Formula **C**.

59. The process of Claim 58, wherein the source of the ammonium ion is ammonium hydroxide.

60. The process of Claim 58 or 59, wherein q and r are each 0.

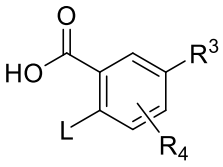
61. The process of any one of Claims 58 to 60, wherein L^v is fluoro.

62. A process for preparing a compound having the Formula **D**:



(**D**),

wherein L is a leaving group and the remaining variables are as described above for Formula **I** in Claim 1, said process comprising reacting a compound having the Formula **F**:



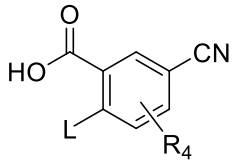
(**F**),

with a chlorinating agent.

63. The process of Claim 62, wherein L is chloro.

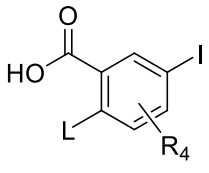
64. The process of Claim 62 or 63, wherein the chlorinating agent is thionyl chloride.

65. A process for preparing a compound having the Formula **G**:



(**G**),

wherein L is a leaving group and R^4 is as described above for Formula **I** in Claim 1, said process comprising reacting a compound having the Formula **H**:



(**H**),

with a palladium catalyst.

66. The process of Claim 65, wherein the palladium catalyst is tris(dibenzylideneacetone)dipalladium(0).

67. The process of Claim 65 or 66, further comprising the addition of a palladium coupling ligand.

68. The process of Claim 67, wherein the palladium coupling ligand is 1,4-bis(diphenylphosphino)butane.

69. The process of any one of Claims 43 to 68, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^a, R^b, R^c, R^d, R^e, and R^f are as defined in any one of Claims 1 to 29, or a combination thereof.

70. The process of Claim 69, wherein the compound of Formula **I** is selected from those in Claim 30 or 31.

71. A compound of any one of Claims 1 to 31, or a pharmaceutically acceptable salt thereof, or the crystalline form of any one of Claims 32 to 39, for use in therapy.