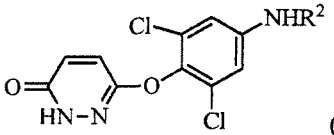
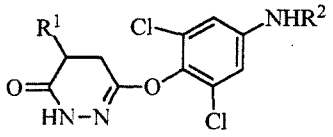
What is claimed is:

1. A synthetic process comprising:

(a) contacting R^1MgX or R^1Li with a compound of Formula

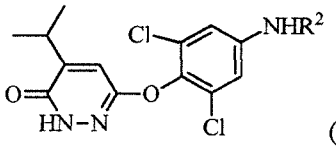


(I) to form a compound of Formula (II):



(II), in which R^1 is isopropyl or isopropenyl, X is halo and R^2 is H or an amine protecting group; and

(b) converting the compound of Formula (II) to a compound of Formula (III):



(III) in the presence of a base when R^1 is isopropenyl or in the presence of an oxidizing agent when R^1 is isopropyl.

2. The process of claim 1, further comprising: (c), when present, removing the amine protecting group R^2 of the compound of Formula (III) to form 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one.

3. The process of claim 1, wherein step (a) is performed by contacting R^1MgX with the compound of Formula (I), in which R^1 is isopropenyl and X is Br.

4. The process of claim 3, wherein step (a) is performed in THF with a volume to weight ratio of THF to the compound of Formula (I) ranging between 7 and 15.

5. The process of claim 3, wherein step (a) is performed in the presence of a Lewis acid.

6. The process of claim 3, wherein the Lewis acid is a lithium halide.

7. The process of claim 1, wherein the base in step (b) is a metal hydroxide.

8. The process of claim 7, wherein the metal hydroxide is potassium hydroxide.

9. The process of claim 1, wherein step (a) is performed by contacting R^1MgX with the compound of Formula (I), in which R^1 is isopropyl and X is Cl.

10. The process of claim 9, wherein step (a) is performed in THF with a volume to weight ratio of THF to the compound of Formula (I) ranging between 7 and 30.

11. The process of claim 1, wherein the oxidizing agent in step (b) is bromine and step (b) is performed in the presence of an acid.

12. The process of claim 1, wherein R^2 is acetyl or benzoyl.

13. The process of claim 12, wherein R^2 is benzoyl.

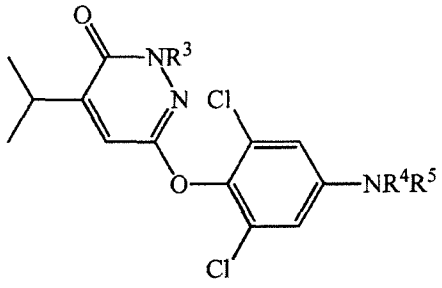
14. The process of claim 1, further comprising providing the compound of Formula (I) by contacting 3,6-dichloropyridazine with 2,6-dichloro-4-aminophenol to form 3,5-dichloro-4-((6-chloropyridazin-3-yl)oxy)aniline, hydrolyzing 3,5-dichloro-4-((6-chloropyridazin-3-yl)oxy)aniline and protecting the amine group of 3,5-dichloro-4-((6-chloropyridazin-3-yl)oxy)aniline either before or after the hydrolysis to form the compound of Formula (I).

15. The process of claim 14, further comprising purifying the compound of Formula (I) before step (a) in an acidic solution at a temperature between 80 and 100 °C.

16. The process of claim 14, wherein the contacting of 3,6-dichloropyridazine with 2,6-dichloro-4-aminophenol is performed in a polar aprotic solvent in the presence of a base at a reaction temperature between 60 and 120 °C.

17. The process of claim 16, wherein the polar aprotic solvent is dimethylacetamide (DMAC), the base is Cs_2CO_3 and the reaction temperature is about 65 °C.

18. The process of claim 2, further comprising: (d) converting 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one to the compound of Formula (IV):



(IV),

wherein

R^3 is H or CH_2R_a, in which R_a is hydroxyl, O-linked amino acid, $-OP(O)(OH)_2$ or

$-OC(O)-R_b$, R_b being lower alkyl, alkoxy, alkyl acid, cycloalkyl, aryl, heteroaryl, or $-(CH_2)_n$-heteroaryl and n being 0 or 1;

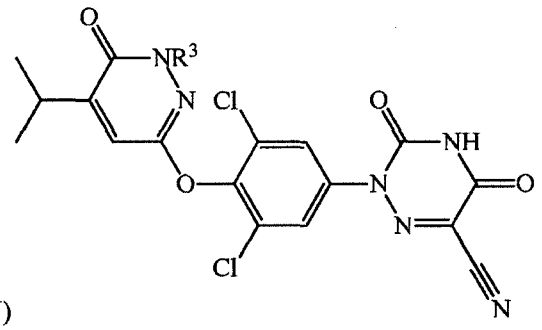
R^4 is H; and

R^5 is CH_2COOH, $C(O)CO_2H$, or an ester or amide thereof, or R^4 and R^5 together are $-N=C(R_c)-C(O)-NH-C(O)-$; in which R_c is H or cyano.

19. The process of claim 18, wherein the compound of Formula (IV) is 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("**Compound A**") and step (d) is performed by contacting 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one with ethyl (2-cyanoacetyl)carbamate and a metal nitrite followed by treatment with potassium acetate in DMAC.

20. The process of claim 19 further comprising forming a morphic form of 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("**Compound A**") (Form I) characterized by an X-ray powder diffraction pattern including peaks at about 10.5, 18.7, 22.9, 23.6, and 24.7 degrees 2θ.

21. The process of claim 18, wherein the compound of Formula (IV) is of Formula



(V) (V), wherein R^3 is CH_2R_a, and step (d) is performed by contacting 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one with ethyl (2-cyanoacetyl)carbamate to form 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("**Compound A**") and converting Compound A to the compound of Formula (V) under a suitable condition.

22. A morphic form of 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("**Compound A**") (Form I) characterized by an X-ray powder diffraction pattern including peaks at about 10.5, 18.7, 22.9, 23.6, and 24.7 degrees 2θ.

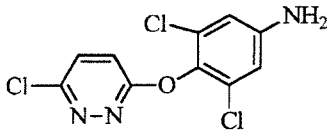
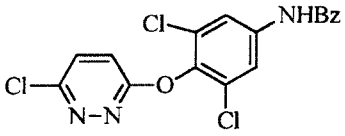
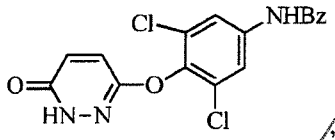
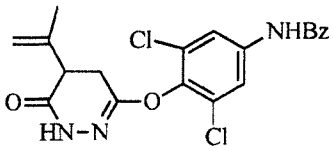
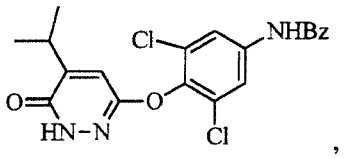
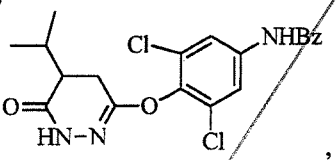
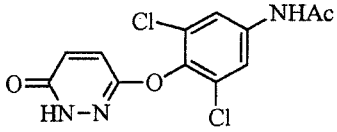
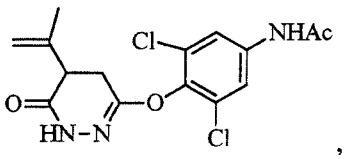
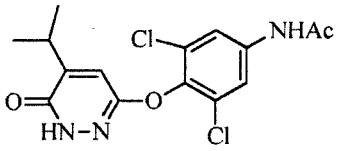
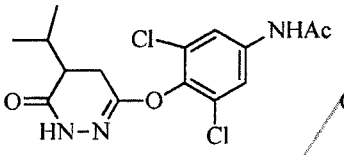
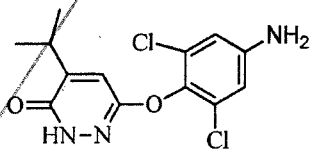
23. The morphic form of claim 22 characterized by an X-ray powder diffraction pattern further including peaks at about 8.2, 11.2, 15.7 16.4, 17.7, 30.0, and 32.2 degrees 2θ.

24. The morphic form of claim 22 characterized by an X-ray powder diffraction pattern substantially similar to that set forth in FIG. 1.

25. The morphic form of claim 22, wherein the morphic form has a purity of greater than 99%.

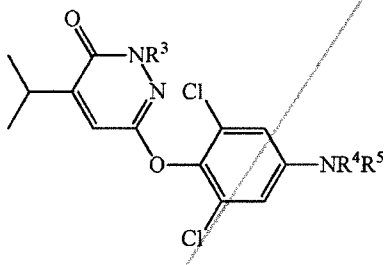
26. A pharmaceutical composition comprising a morphic form of claim 22 and a pharmaceutically acceptable carrier.

27. A compound selected from:

, and a salt thereof.

28. A pharmaceutical composition for treating a resistance to thyroid hormone (RTH) in a subject in need thereof, comprising a therapeutically effective amount of a compound of Formula (IV):



(IV),

wherein

R^3 is H or CH_2R_a, in which R_a is hydroxyl, O-linked amino acid, $-OP(O)(OH)_2$ or $-OC(O)-R_b$, R_b being lower alkyl, alkoxy, alkyl acid, cycloalkyl, aryl, heteroaryl, or $-(CH_2)_n$-heteroaryl and n being 0 or 1;

R^4 is H; and

R^5 is CH_2COOH, $C(O)CO_2H$, or an ester or amide thereof, or R^4 and R^5 together are $-N=C(R_c)-C(O)-NH-C(O)-$; in which R_c is H or cyano;

wherein said subject has at least one TRβ mutation.

29. The pharmaceutical composition of claim 28 for treating RTH, wherein said compound is 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("**Compound A**").

30. The pharmaceutical composition of claim 28 for treating RTH, wherein said subject has obesity, hyperlipidemia, hypercholesterolemia, diabetes, non-alcoholic steatohepatitis, fatty liver, bone disease, thyroid axis alteration, atherosclerosis, a cardiovascular disorder, tachycardia, hyperkinetic behavior, hypothyroidism, goiter, attention deficit hyperactivity disorder, learning disabilities, mental retardation, hearing loss, delayed bone age, neurologic or psychiatric disease or thyroid cancer.

31. The pharmaceutical composition of claim 28 for treating RTH, wherein said TRβ mutation is selected from the group consisting of a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 234 of SEQ ID NO: 1 (A234T); a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 243 of SEQ ID NO: 1 (R243Q); a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 316 of SEQ ID NO: 1 (R316H); and a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 317 of SEQ ID NO: 1 (A317T).

32. A process of preparing the morphic form of claim 22, the process comprising:

heating a mixture comprising a solvent and a sample containing Compound A at a first temperature, and

cooling the mixture to a second temperature that is lower than the first temperature so as to obtain the morphic form of claim 22, wherein the solvent is selected from ethanol, isopropanol, methyl isobutyl ketone and a combination thereof.

33. The process of claim 32, wherein the first temperature is between about 60 °C and about 80 °C.

34. The process of claim 32 or 33, wherein the second temperature is between about
0 °C and about 60 °C.

35. The process of claim 34, wherein the second temperature is between about 40 °C and about 60 °C.

36. The process of claim 34, wherein the solvent is ethanol or methyl isobutyl ketone.

37. The process of claim 32 or 33, wherein the sample containing Compound A comprises a solvate of Compound A.

38. The process of claim 37, wherein the solvate of Compound A is an ethanol solvate, a methyl isobutyl ketone solvate, a *N*,*N*-dimethylacetamide solvate, or a hydrate.

39. The process of claim 32 or 33, further comprising, after cooling the mixture, filtering the mixture to obtain a filter cake.

40. The process of claim 39, further comprising, after filtering the mixture, rinsing the filter cake with an organic solvent to obtain a rinsed filter cake.

41. The process of claim 40, wherein the organic solvent is an alcohol.

42. The process of claim 41, wherein the alcohol is ethanol.

43. The process of claim 41, further comprising, after rinsing the filter cake, drying the rinsed filter cake to obtain Form I of Compound A.

44. The process of claim 43, wherein the rinsed filter cake is dried.

45. Form I of Compound A prepared by the process of claim 44.

46. Form I of claim 45, being substantially free of solvates of Compound A.

47. Form I of claim 45, having a purity of 95% or greater.

48. Form I of claim 45, containing about 5% or less of any solvates of Compound A.

49. A process of preparing a morphic form of claim 22, the process comprising:

heating a mixture comprising a solvent and a sample containing Compound A at a first temperature, wherein the solvent is selected from ethanol, isopropanol, methyl isobutyl ketone and a combination thereof;

cooling the mixture to a second temperature that is lower than the first temperature;

filtering the mixture to obtain a filter cake;

rinsing the filter cake with an organic solvent to obtain a rinsed filter cake; and

drying the rinsed filter cake to obtain the morphic form of claim 22.

50. A process of preparing a morphic form of claim 22, the process comprising:

heating a mixture comprising ethanol and a sample containing Compound A at a first temperature;

cooling the mixture to a second temperature that is lower than the first temperature but greater than about 40 °C;

filtering the mixture at a temperature not lower than about 40 °C to obtain a filter cake;

rinsing the filter cake at a temperature not lower than about 40 °C with ethanol to obtain a rinsed filter cake; and

drying the rinsed filter cake at a temperature not lower than about 40 °C to obtain the morphic form of claim 22.

51. Form I of Compound A prepared by the process of 50.

Claims:

1. A morphic form of 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("Compound A") (Form I) characterized by an X-ray powder diffraction pattern including peaks at about 10.5, 18.7, 22.9, 23.6, and 24.7 degrees 2θ.

2. The morphic form of claim 1 characterized by an X-ray powder diffraction pattern further including peaks at about 8.2, 11.2, 15.7 16.4, 17.7, 30.0, and 32.2 degrees 2θ.

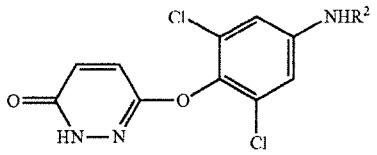
3. The morphic form of claim 1 characterized by an X-ray powder diffraction pattern substantially similar to that set forth in FIG. 1.

4. The morphic form of claim 1, wherein the morphic form has a purity of 95% or greater.

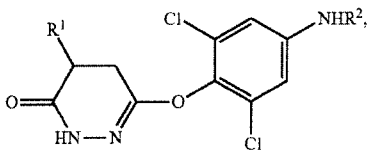
5. A pharmaceutical composition comprising a morphic form of claim 1 and a pharmaceutically acceptable carrier.

6. A synthetic process comprising:

(a) contacting R^1MgX or R^1Li with a compound of Formula (I):

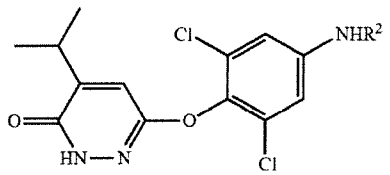


to form a compound of Formula (II):



in which R^1 is isopropyl or isopropenyl, X is halo and R^2 is H or an amine protecting group; and

(b) converting the compound of Formula (II) to a compound of Formula (III):



in the presence of a base when R^1 is isopropenyl or in the presence of an oxidizing agent when R^1 is isopropyl.

7. The process of claim 6, further comprising: (c), when present, removing the amine protecting group R^2 of the compound of Formula (III) to form 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one.

8. The process of claim 6, wherein step (a) is performed by contacting R^1MgX with the compound of Formula (I), in which R^1 is isopropenyl and X is Br; or step (a) is performed by contacting R^1MgX with the compound of Formula (I), in which R^1 is isopropyl and X is Cl.

9. The process of claim 6, wherein the oxidizing agent in step (b) is bromine and step (b) is performed in the presence of an acid.

10. The process of claim 6, wherein R^2 is acetyl or benzoyl.

11. The process of claim 7, further comprising: (d) converting 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one to 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile ("Compound A") by contacting 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one with ethyl (2-cyanoacetyl)carbamate and a metal nitrite followed by treatment with potassium acetate in DMAC.

12. A process of preparing the preparing the morphic form of claim 1, the process comprising:

heating a mixture comprising a solvent and Compound A at a first temperature, and

cooling the mixture to a second temperature that is lower than the first temperature so as to obtain the morphic form of claim 1, wherein the solvent is selected from ethanol, isopropanol, methyl isobutyl ketone and a combination thereof.

13. The process of claim 12, wherein the first temperature is between about 60° C. and about 80° C.

14. The process of claim 12, wherein the second temperature is between about 0° C. and about 60° C.

15. The process of claim 12, wherein the solvent is ethanol or methyl isobutyl ketone.

16. A process of preparing a morphic form of claim 1, the process comprising:

heating a mixture comprising a solvent and Compound A at a first temperature, wherein the solvent is selected from ethanol, isopropanol, methyl isobutyl ketone and a combination thereof;

cooling the mixture to a second temperature that is lower than the first temperature;

filtering the mixture to obtain a filter cake;

rinsing the filter cake with an organic solvent to obtain a rinsed filter cake; and

drying the rinsed filter cake to obtain the morphic form of claim 1.

17. A process of preparing a morphic form of claim 1, the process comprising:

heating a mixture comprising ethanol and Compound A at a first temperature;

cooling the mixture to a second temperature that is lower than the first temperature but greater than about 40° C.;

filtering the mixture at a temperature not lower than about 40° C. to obtain a filter cake;

rinsing the filter cake at a temperature not lower than about 40° C. with ethanol to obtain a rinsed filter cake; and

drying the rinsed filter cake at a temperature not lower than about 40° C. to obtain the morphic form of claim 1.