METHODS FOR PREPARING PYRIDAZINONE DERIVATIVES

RELATED APPLICATIONS

[001] This application claims priority to, and the benefit of, U.S. Application Nos. 63/104,898, filed October 23, 2020, and 63/150,616, filed on February 18, 2021, the entire contents of each of which are incorporated herein by reference.

FIELD OF INVENTION

[002] The invention relates to methods for preparing pyridazinone derivatives.

BACKGROUND

[003] Thyroid hormones are critical for normal growth and development and for maintaining metabolic homeostasis. Circulating levels of thyroid hormones are tightly regulated by feedback mechanisms in the hypothalamus/pituitary/thyroid (HPT) axis. Thyroid dysfunction leading to hypothyroidism or hyperthyroidism clearly demonstrates that thyroid hormones exert profound effects on cardiac function, body weight, metabolism, metabolic rate, body temperature, cholesterol, bone, muscle, and behavior.

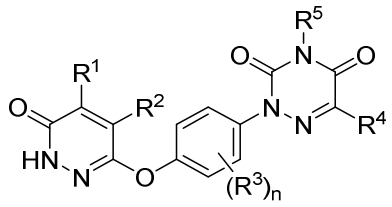
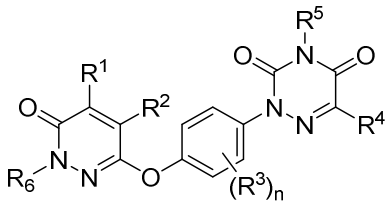
[004] The development of thyroid hormone analogs which avoid the undesirable effects of hyperthyroidism and hypothyroidism while maintaining the beneficial effects of thyroid hormones would open new avenues of treatment for patients with metabolic disease such as obesity, hyperlipidemia, hypercholesterolemia, diabetes and other disorders and diseases such as liver steatosis and Nonalcoholic steatohepatitis (NASH), atherosclerosis, cardiovascular diseases, hypothyroidism, thyroid cancer, thyroid diseases, resistance to thyroid hormone and related disorders and diseases.

[005] There exists an unmet need to develop new methods of preparing pyridazinone compounds as thyroid hormone analogs.

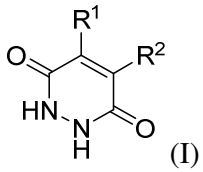
SUMMARY

[006] The present invention, in part, provides methods for synthesizing thyroid hormone analogs such as pyridazinone compounds and salts thereof. For example, the present invention provides non-Grignard methods for synthesizing thyroid hormone analogs such as pyridazinone compounds and salts thereof. The present invention also relates to intermediates for synthesizing pyridazinone compounds or salts thereof.

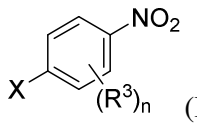
[007] Invention provides a method of synthesizing a compound of formula V or Va:


(V) or

(V-a).

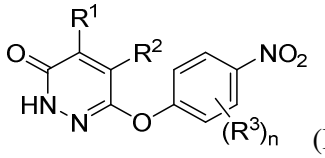
[008] In one aspect, the present disclosure provides a method comprising contacting a compound of formula (I), a tautomer or a salt thereof:


(I)

with a compound of formula (II) or a salt thereof:


(II)

in a first organic solvent in the presence of a base, to form a compound of formula (III) or a salt thereof:


(III),

wherein:

R^1 and R^2 are each independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_4-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^1 and R^2 come together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^3 is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -

$C(=O)OR^b$, $-OC(=O)OR^b$, $-C(=O)NR^bR^c$, $-OC(=O)NR^bR^c$, $-NR^bC(=O)NR^bR^c$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^bR^c$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^a is independently C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, or C_1-C_6 haloalkyl;

each R^b is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^c is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

X is halogen; and

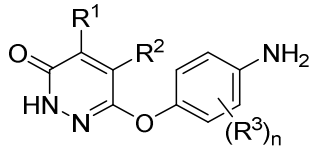
n is 0, 1, 2, 3, or 4.

[009] In some embodiments, the first organic solvent comprises dimethylformamide (DMF), dimethylacetamide (DMAC), dimethyl sulfoxide (DMSO), acetonitrile, tetrahydrofuran (THF), dichloromethane (DCM), dioxane, or acetone.

[010] In some embodiments, the base comprises sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), potassium carbonate (K_2CO_3), or potassium bicarbonate ($KHCO_3$).

[011] In some embodiments, the contacting occurs at room temperature or above room temperature.

[012] In one aspect, the present disclosure provides a method comprising contacting the compound of formula (III) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV) or a salt thereof:

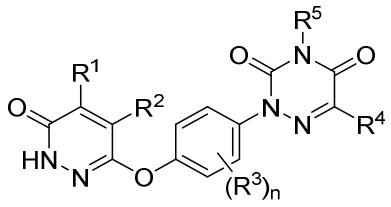


(IV).

[013] In some embodiments, the reducing agent comprises hydrogen (H_2) gas and palladium on carbon (Pd/C), H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride.

[014] In some embodiments, the contacting occurs at room temperature or above room temperature.

[015] In one aspect, the present disclosure provides a method comprising contacting the compound of formula (IV) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ to form a compound of formula (V) or a salt thereof:



(V),

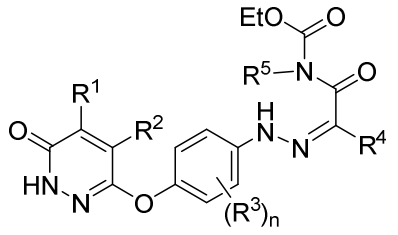
wherein:

R^4 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally

substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[016] In some embodiments, the method comprises contacting a compound of formula (IV) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ in the presence of an oxidizing agent and an acid to form a compound of formula (IV-int) or a salt thereof:

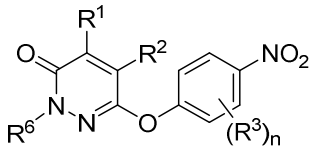


(IV-int).

[017] In some embodiments, the oxidizing agent is sodium nitrite ($NaNO_2$) or potassium nitrite (KNO_2). In some embodiments, the acid is hydrochloric acid (HCl) or acetic acid (AcOH).

[018] In some embodiments, the method comprises contacting the compound of formula (IV-int) with a base to form a compound of formula (V). In some embodiments, the base is sodium acetate (NaOAc) or potassium acetate (KOAc).

[019] In one aspect, the present disclosure provides a method comprising contacting the compound of formula (III) or a salt thereof with R^6X to form a compound of formula (III-a) or a salt thereof:



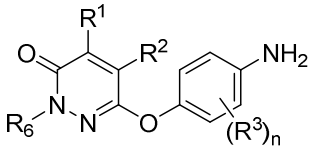
(III-a),

wherein:

R^6 is -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

X is as defined herein for formula (II).

[020] In one aspect, the present disclosure provides a method comprising contacting the compound of formula (III-a) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV-a) or a salt thereof:

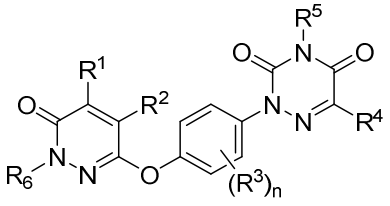


(IV-a).

[021] In some embodiments, the reducing agent comprises H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride.

[022] In some embodiments, the contacting occurs at room temperature or above room temperature.

[023] In one aspect, the present disclosure provides a method comprising contacting the compound of formula (IV-a) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ to form a compound of formula (V-a) or a salt thereof:



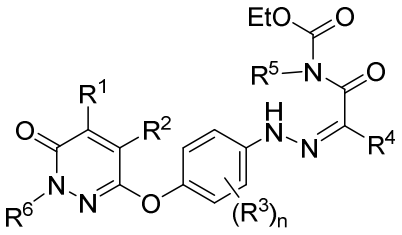
(V-a)

wherein:

R^4 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[024] In some embodiments, the method comprises contacting a compound of formula (IV-a) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ in the presence of an oxidizing agent and an acid to form a compound of formula (IV-a-int) or a salt thereof:

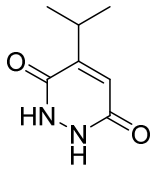


(IV-a-int).

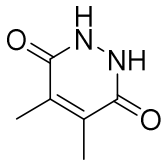
[025] In some embodiments, the oxidizing agent is $NaNO_2$ or KNO_2. In some embodiments, the acid is HCl or AcOH.

[026] In some embodiments, the method comprises contacting the compound of formula (IV-a-int) with a base to form a compound of formula (V-a). In some embodiments, the base is NaOAc or KOAc.

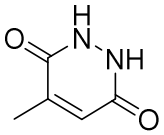
[027] In some embodiments, the compound of formula (I) is 4-isopropylpyridazine-3,6-diol (compound 1-1), 4,5-dimethyl-1,2-dihydropyridazine-3,6-dione (compound 2-1), 4-methyl-1,2-dihydropyridazine-3,6-dione (compound 3-1), 4-phenyl-1,2-dihydropyridazine-3,6-dione (compound 4-1), 4-(trifluoromethyl)-1,2-dihydropyridazine-3,6-dione (compound 5-1), 2,3,5,6,7,8-hexahydrophthalazine-1,4-dione (compound 6-1), or 2,3-dihydrophthalazine-1,4-dione (compound 7-1):



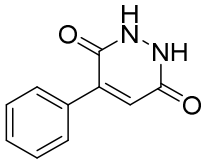
(compound 1-1),



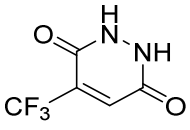
(compound 2-1),



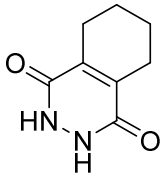
(compound 3-1),



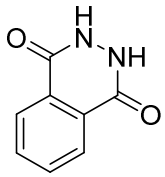
(compound 4-1),



(compound 5-1),

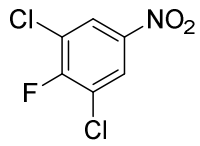


(compound 6-1), or

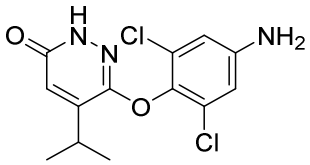
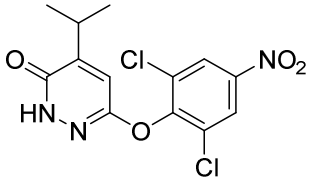
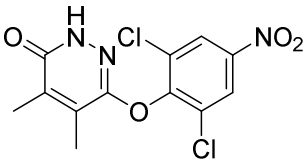
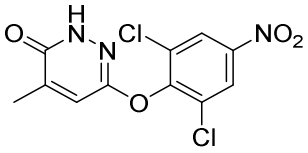
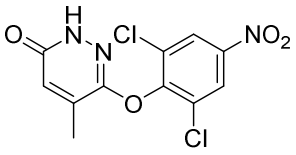
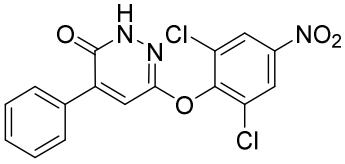
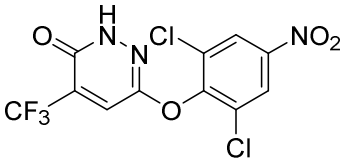
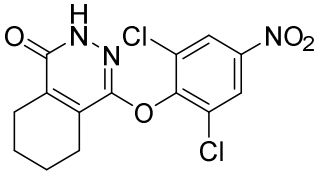
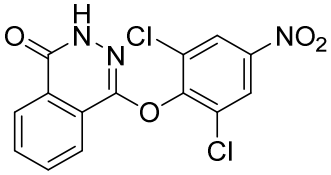


(compound 7-1).

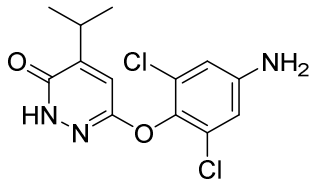
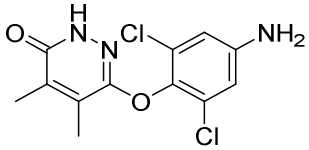
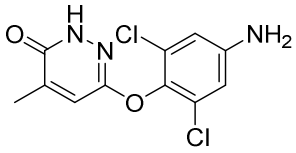
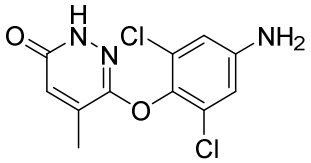
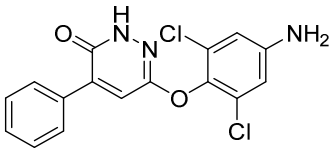
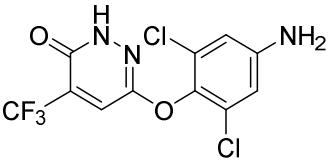
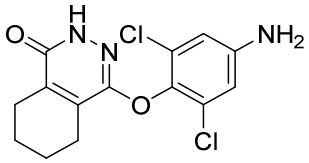
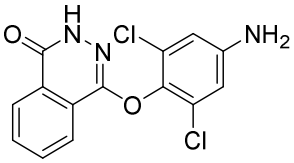
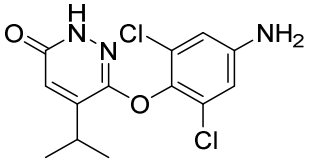
[028] In some embodiments, the compound of formula (II) is 1,3-dichloro-2-fluoro-5-nitrobenzene (compound 1-2):


(compound 1-2).

[029] In some embodiments, the compound of formula (III) is 6-(4-amino-2,6-dichlorophenoxy)-5-isopropylpyridazin-3(2H)-one (compound 1-3), 6-(2,6-dichloro-4-nitrophenoxy)-4-isopropylpyridazin-3(2H)-one (compound 1-4), 6-(2,6-dichloro-4-nitrophenoxy)-4,5-dimethylpyridazin-3(2H)-one (compound 2-2), 6-(2,6-dichloro-4-nitrophenoxy)-4-methylpyridazin-3(2H)-one (compound 3-2), 6-(2,6-dichloro-4-nitrophenoxy)-5-methylpyridazin-3(2H)-one (compound 3-3), 6-(2,6-dichloro-4-nitrophenoxy)-4-phenylpyridazin-3(2H)-one (compound 4-2), 6-(2,6-dichloro-4-nitrophenoxy)-4-(trifluoromethyl)pyridazin-3(2H)-one (compound 5-2), 4-(2,6-dichloro-4-nitrophenoxy)-5,6,7,8-tetrahydrophthalazin-1(2H)-one (compound 6-2), or 4-(2,6-dichloro-4-nitrophenoxy)phthalazin-1(2H)-one (compound 7-2):

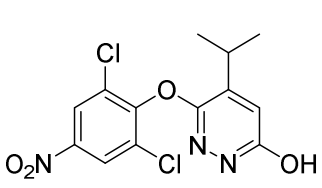
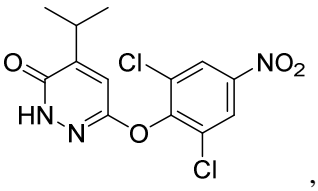
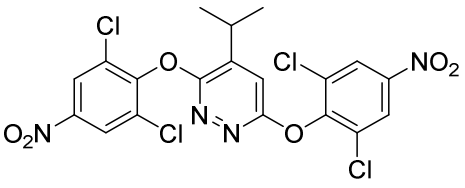
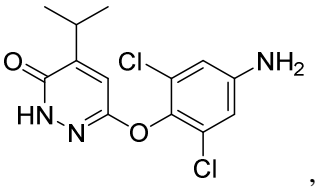
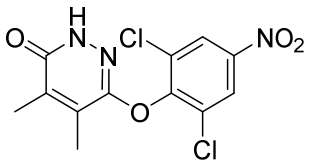
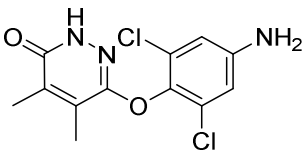
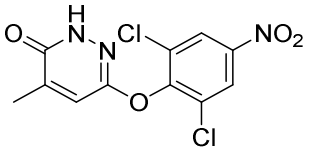
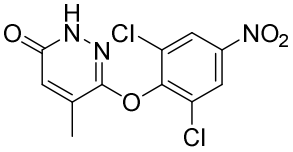
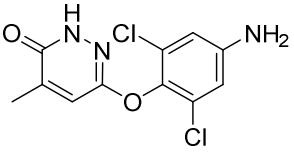
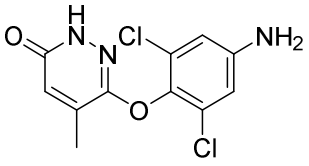
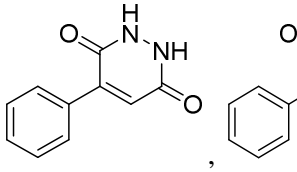
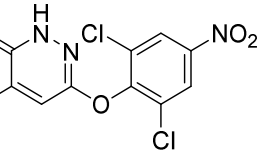
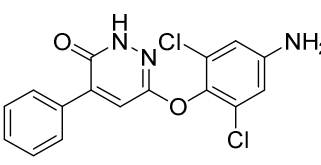
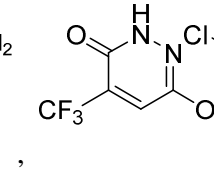
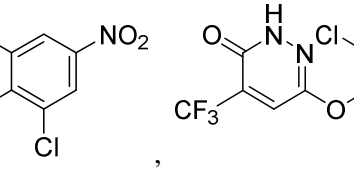
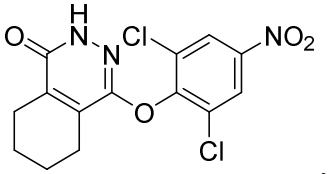
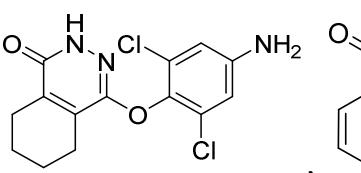
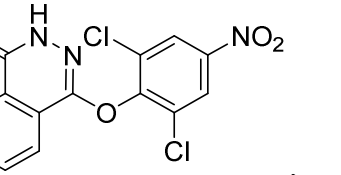
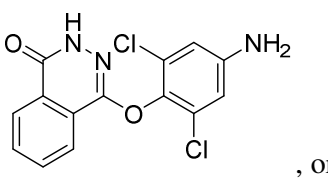
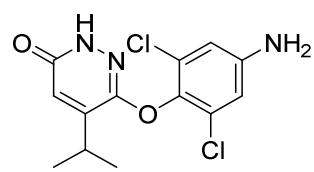

(compound 1-3),

(compound 1-4),

(compound 2-2),

(compound 3-2),

(compound 3-3),

(compound 4-2),

(compound 5-2),

(compound 6-2), or

(compound 7-2).

[030] In some embodiments, the compound of formula (IV) is 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (Int. 7), 6-(4-amino-2,6-dichlorophenoxy)-4,5-dimethylpyridazin-3(2H)-one (compound 2-3), 6-(4-amino-2,6-dichlorophenoxy)-4-methylpyridazin-3(2H)-one (compound 3-4), 6-(4-amino-2,6-dichlorophenoxy)-5-methylpyridazin-3(2H)-one (compound 3-5), 6-(4-amino-2,6-dichlorophenoxy)-4-phenylpyridazin-3(2H)-one (compound 4-3), 6-(4-amino-2,6-dichlorophenoxy)-4-(trifluoromethyl)pyridazin-3(2H)-one (compound 5-3), 4-(4-amino-2,6-dichlorophenoxy)-5,6,7,8-tetrahydrophthalazin-1(2H)-one (compound 6-3), 4-(4-amino-2,6-dichlorophenoxy)phthalazin-1(2H)-one (compound 7-3), or 6-(4-amino-2,6-dichlorophenoxy)-5-isopropylpyridazin-3(2H)-one (compound 8-1):


(Int. 7),

(compound 2-3),

(compound 3-4),

(compound 3-5),

(compound 4-3),

(compound 5-3),

(compound 6-3),

(compound 7-3), or

(compound 8-1).

[031] In some embodiments, the compound of formula (V) 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 (MGL-3196).

[032] In one aspect, the present disclosure provides a compound having the structure of

 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , or .

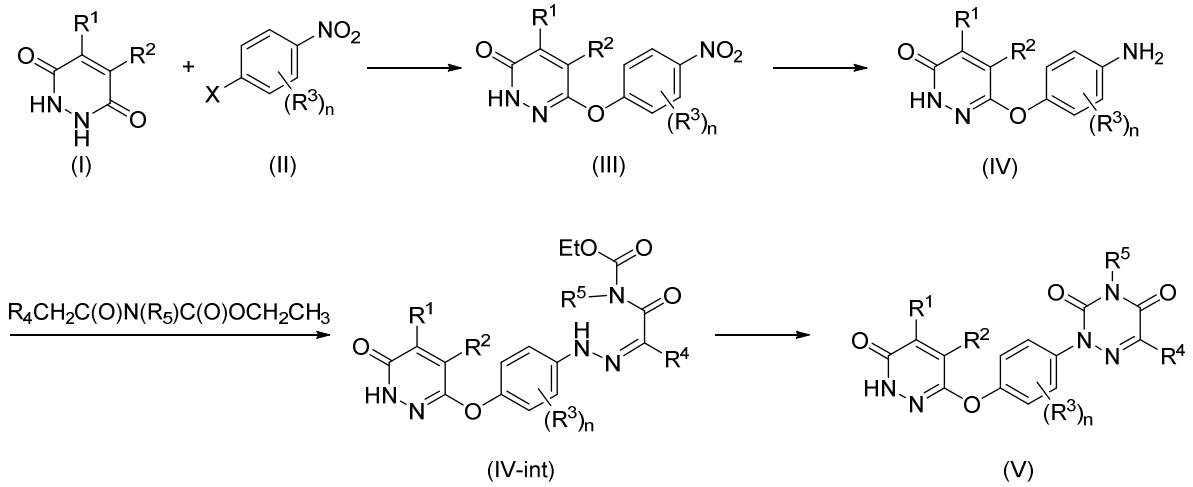
DETAILED DESCRIPTION

[033] The present disclosure provides non-Grignard methods for preparing pyridazinone derivatives. As compared to Grignard methods for preparing pyridazinone derivatives, the non-Grignard methods described herein are advantageous at least because they avoid the

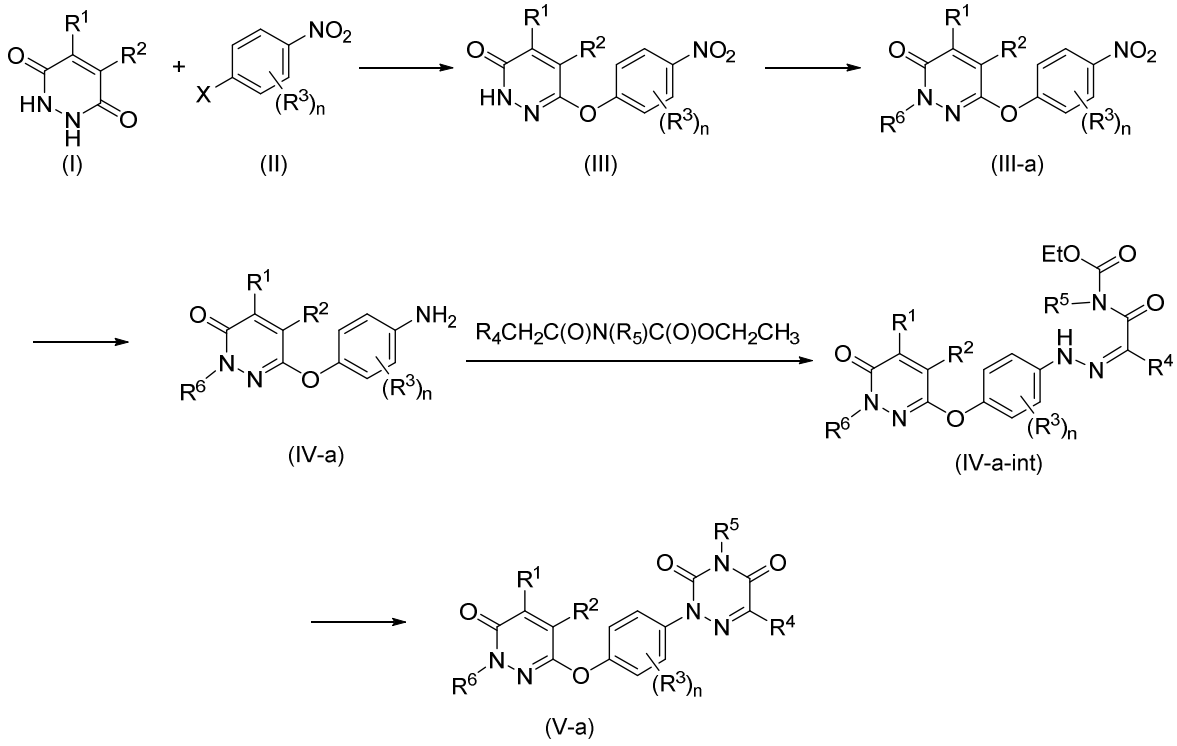
requirements to use hazardous, expensive Grignard reagents to manufacture the intermediates for the production of pyridazinone derivatives such as MGL-3196.

[034] Some aspects of the present disclosure relate to one or more steps in a synthesis scheme according to Scheme 1, Scheme 2, or Scheme 3 below:

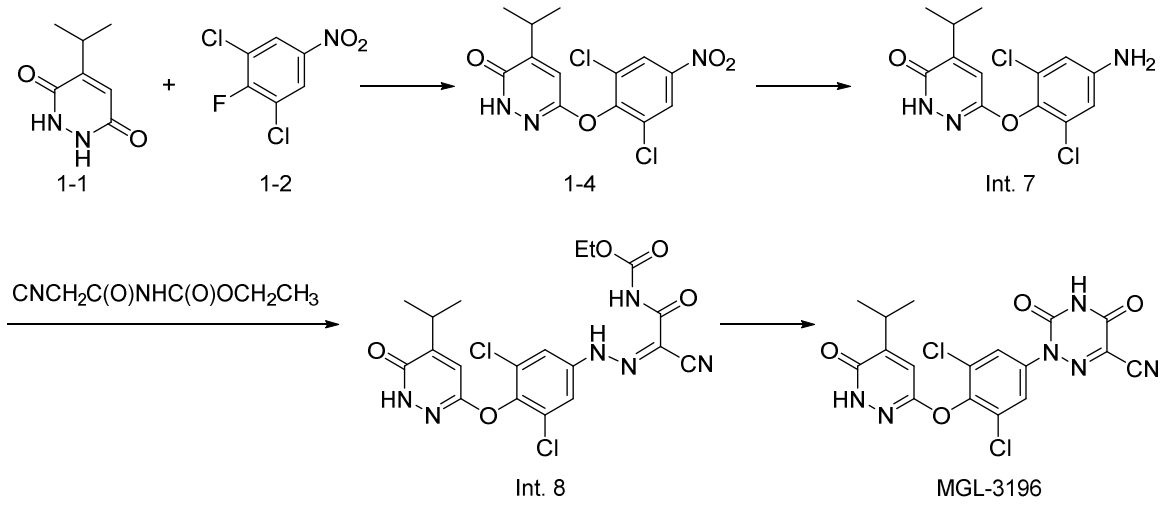
Scheme 1:



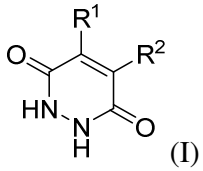
Scheme 2:



Scheme 3:

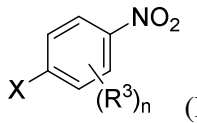


[035] In one aspect, the present disclosure provides a method comprising contacting a compound of formula (I), a tautomer or a salt thereof:



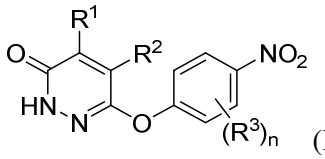
(I)

with a compound of formula (II) or a salt thereof:



(II)

in a first organic solvent in the presence of a base, to form a compound of formula (III) or a salt thereof:



(III),

wherein:

R^1 and R^2 are each independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_4-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^1 and R^2 come together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen,

-CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^3 is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^a is independently C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, or C_1-C_6 haloalkyl;

each R^b is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^c is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

X is halogen; and

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

[036] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[037] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^1 is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[038] In some embodiments, R^1 is hydrogen or deuterium. In some embodiments, R^1 is hydrogen.

[039] In some embodiments, R^1 is halogen, -CN, -OH, -OR^a, -NR^bR^c, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^bR^c, C_4-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_4-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[040] In some embodiments, R^1 is C_4-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[041] In some embodiments, R^1 is C_4-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more halogen. In some embodiments, R^1 is C_1-C_6 deuteroalkyl.

[042] In some embodiments, R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

[043] In some embodiments, R^1 is C_1-C_6 alkyl. In some embodiments, R^1 is methyl. In some embodiments, R^1 is ethyl. In some embodiments, R^1 is propyl. In some embodiments, R^1 is butyl. In some embodiments, R^1 is isopropyl. In some embodiments, R^1 is iso-butyl. In some embodiments, R^1 is sec-butyl. In some embodiments, R^1 is tert-butyl. In some embodiments, R^1 is pentyl. In some embodiments, R^1 is iso-pentyl. In some embodiments, R^1 is hexyl. In some embodiments, R^1 is iso-hexyl.

[044] In some embodiments, R^1 is C_2-C_6 alkenyl. In some embodiments, R^1 is C_2 alkenyl. In some embodiments, R^1 is C_3 alkenyl. In some embodiments, R^1 is C_4 alkenyl. In some embodiments, R^1 is C_5 alkenyl. In some embodiments, R^1 is C_6 alkenyl.

[045] In some embodiments, R^1 is C_2-C_6 alkynyl. In some embodiments, R^1 is C_2 alkynyl. In some embodiments, R^1 is C_3 alkynyl. In some embodiments, R^1 is C_4 alkynyl. In some embodiments, R^1 is C_5 alkynyl. In some embodiments, R^1 is C_6 alkynyl.

[046] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^2 is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^bR^c$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[047] In some embodiments, R^2 is hydrogen, deuterium, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is deuterium.

[048] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^3 is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^bR^c$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[049] In some embodiments, R^1 and R^2 come together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, R^1 and R^2 come together to form a cycloalkyl. In some embodiments, R^1 and R^2 come together to form an aryl. In some embodiments, R^1 and R^2 come together to form a heterocycloalkyl. In some embodiments, R^1 and R^2 come together to form a heteroaryl.

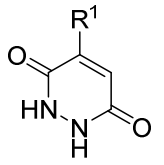
[050] In some embodiments, R^1 and R^2 come together to form a cycloalkyl. In some embodiments, R^1 and R^2 come together to form a 6-membered cycloalkyl.

[051] In some embodiments, R^1 and R^2 come together to form an aryl. In some embodiments, R^1 and R^2 come together to form a 6-membered aryl.

[052] In some embodiments, each R^3 is independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In some embodiments, each R^3 is independently halogen, such as halogen, fluorine, chlorine, bromine, and iodine. In some embodiments, one of R^3 is deuterium. In some embodiments, each R^3 is independently hydrogen, deuterium, halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In some embodiments, each R^3 is independently deuterium, halogen, or C_1-C_6 alkyl. In some embodiments, each R^3 is independently deuterium or halogen.

[053] In some embodiments, X is halogen. In some embodiments, X is fluorine. In some embodiments, X is chlorine. In some embodiments, X is bromine. In some embodiments, X is iodine.

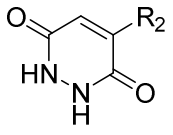
[054] In some embodiments, the compound of formula (I) is a compound of formula (I-a):



(I-a),

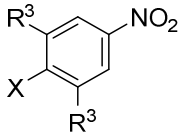
a tautomer or a salt thereof, wherein R^1 is as described herein for formula (I).

[055] In some embodiments, the compound of formula (I) is a compound of formula (I-b):


(I-b)

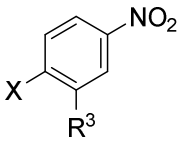
a tautomer, or a salt thereof, wherein R^2 is as described herein for formula (I).

[056] In some embodiments, the compound of formula (II) is a compound of formula (II-a):


(II-a)

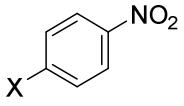
or a salt thereof, wherein X and R^3 is as described herein for formula (II).

[057] In some embodiments, the compound of formula (II) is a compound of formula (II-b):


(II-b)

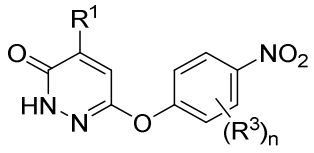
or a salt thereof, wherein X and R^3 is as described herein for formula (II).

[058] In some embodiments, the compound of formula (II) is a compound of formula (II-c):


(II-c)

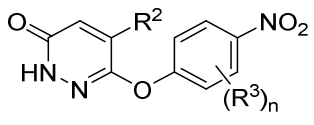
or a salt thereof, wherein X is as described herein for formula (II).

[059] In some embodiments, the compound of formula (III) is a compound of formula (III-b):


(III-b)

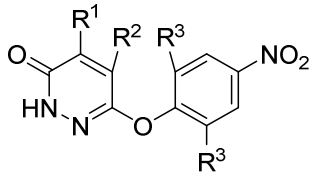
or a salt thereof, wherein R^1, R^3, and n are as described herein for formula (III).

[060] In some embodiments, the compound of formula (III) is a compound of formula (III-d):


(III-d)

or a salt thereof, wherein R^2, R^3, and n are as described herein for formula (III).

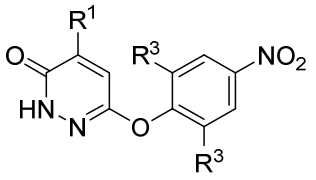
[061] In some embodiments, the compound of formula (III) is a compound of formula (III-f):



(III-f)

or a salt thereof, wherein R^1, R^2, and R^3 are as described herein for formula (III).

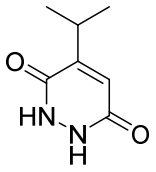
[062] In some embodiments, the compound of formula (III) is a compound of formula (III-h):



(III-h)

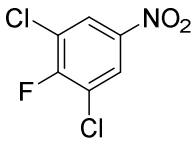
or a salt thereof, wherein R^1 and R^3 are as described herein for formula (III).

[063] In some embodiments, a compound of formula (I) is 4-isopropylpyridazine-3,6-diol (compound 1-1):



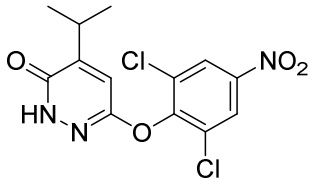
(compound 1-1).

[064] In some embodiments, a compound of formula (II) is 1,3-dichloro-2-fluoro-5-nitrobenzene (compound 1-2):



(compound 1-2).

[065] In some embodiments, a compound of formula (III) is 6-(2,6-dichloro-4-nitrophenoxy)-4-isopropylpyridazin-3(2H)-one (compound 1-4):



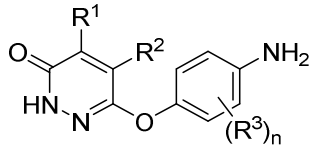
(compound 1-4).

[066] The first organic solvent used in the synthesis of the compound of formula (III) can comprise DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a

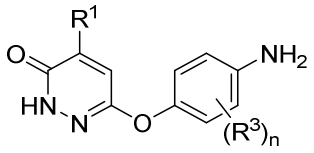
combination thereof. In some embodiments, the first organic solvent used in the synthesis of the compound of formula (III) is DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a combination thereof. In some embodiments, the first organic solvent comprises DMF. In some embodiments, the first organic solvent is DMF.

[067] The base used in the synthesis of the compound of formula (III) can comprise Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, or a combination thereof. In some embodiments, the base used in the synthesis of the compound of formula (III) is Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, or a combination thereof. In some embodiments, the base is added as a solid.

[068] In some embodiments, the method further comprises contacting the compound of formula (III) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV) or a salt thereof:

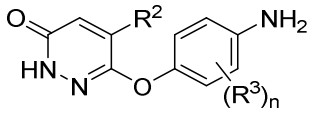

(IV).

[069] In some embodiments, the compound of formula (IV) is a compound of formula (IV-b):


(IV-b)

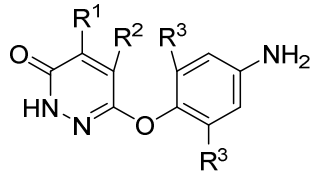
or a salt thereof, wherein R^1, R^3, and n are as described herein for formula (IV).

[070] In some embodiments, the compound of formula (IV) is a compound of formula (IV-d):


(IV-d)

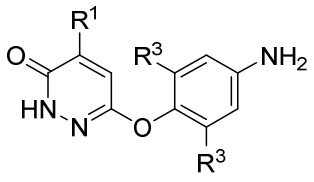
or a salt thereof, wherein R^2, R^3, and n are as described herein for formula (IV).

[071] In some embodiments, the compound of formula (IV) is a compound of formula (IV-f):


(IV-f)

or a salt thereof, wherein R^1, R^2, and R^3 are as described herein for formula (IV).

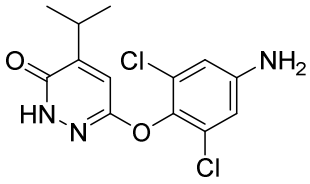
[072] In some embodiments, the compound of formula (IV) is a compound of formula (IV-h):



(IV-h)

or a salt thereof, wherein R^1 and R^3 are as described herein for formula (IV).

[073] In some embodiments, the compound of formula (IV) is 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (Int. 7):

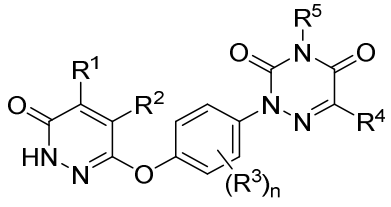


(Int. 7).

[074] The second organic solvent used in the synthesis of the compound of formula (IV) can comprise DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a combination thereof. The second organic solvent used in the synthesis of the compound of formula (IV) is DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a combination thereof. In some embodiments, the second organic solvent comprises THF. In some embodiments, the second organic solvent is THF.

[075] In some embodiments, the reducing agent used in the synthesis of the compound of formula (IV) can comprise H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride. In some embodiments, the reducing agent used in the synthesis of the compound of formula (IV) is H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride. In some embodiments, the reducing agent comprises H_2 gas and Pd/C. In some embodiments, the reducing agent is H_2 gas and Pd/C.

[076] In some embodiments, the method further comprises contacting the compound of formula (IV) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ to form a compound of formula (V) or a salt thereof:



(V),

wherein:

R^4 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[077] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^4 is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[078] In some embodiments, R^4 is hydrogen, deuterium or halogen.

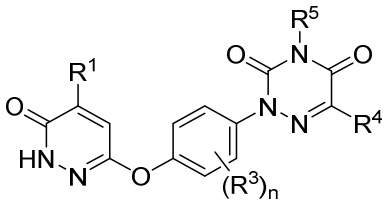
[079] In some embodiments, R^4 is -CN.

[080] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^5 is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[081] In some embodiments, R^5 is hydrogen or C_1-C_6 alkyl.

[082] In some embodiments, R^5 is hydrogen.

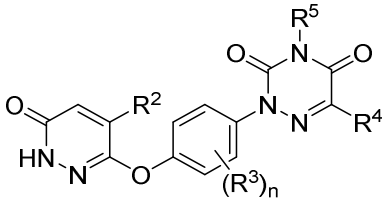
[083] In some embodiments, the compound of formula (V) is a compound of formula (V-b):



(V-b)

or a salt thereof, wherein R^1, R^3, R^4, R^5, and n are as described herein for formula (V).

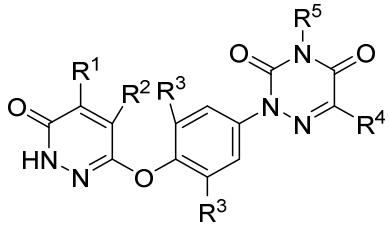
[084] In some embodiments, the compound of formula (V) is a compound of formula (V-d):



(V-d)

or a salt thereof, wherein R^2, R^3, R^4, R^5, and n are as described herein for formula (V).

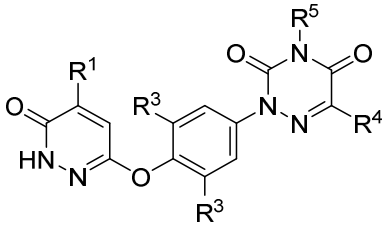
[085] In some embodiments, the compound of formula (V) is a compound of formula (V-f):



(V-f)

or a salt thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as described herein for formula (V).

[086] In some embodiments, the compound of formula (V) is a compound of formula (V-h):



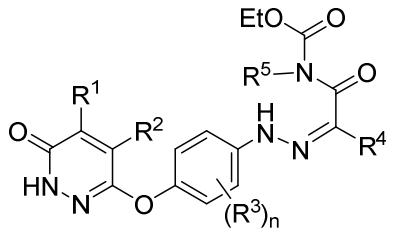
(V-h)

or a salt thereof, wherein R^1, R^3, R^4, and R^5 are as described herein for formula (V).

[087] In some embodiments, $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ is $CNCH_2C(O)NHC(O)OCH_2CH_3$.

[088] In some embodiments, a compound of formula (V) 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 (MGL-3196).

[089] In some embodiments, prior to the formation of a compound of formula (V), the method further comprises contacting a compound of formula (IV) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$, as described above, in the presence of an oxidizing agent and an acid to form a compound of formula (IV-int) or a salt thereof:

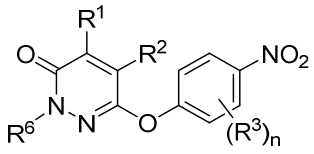


(IV-int).

[090] In some embodiments, the oxidizing agent used in the synthesis of the compound of formula (IV-int) can comprise $NaNO_2$, KNO_2, or a combination thereof. In some embodiments, the oxidizing agent used in the synthesis of the compound of formula (IV-int) is $NaNO_2$, KNO_2, or a combination thereof. In some embodiments, the acid used in the synthesis of the compound of formula (V-int) can comprise HCl, AcOH, or a combination thereof. In some embodiments, the acid used in the synthesis of the compound of formula (V-int) is HCl, AcOH, or a combination thereof.

[091] In some embodiments, the method further comprises contacting the compound of formula (IV-int) with a base to form a compound of formula (V). In some embodiments, the base used in the synthesis of the compound of formula (V) can comprise sodium acetate (NaOAc), potassium acetate (KOAc), or a combination thereof. In some embodiments, the base used in the synthesis of the compound of formula (V) is NaOAc, KOAc, or a combination thereof.

[092] In some embodiments, the method further comprises contacting the compound of formula (III) or a salt thereof with R^6X to form a compound of formula (III-a) or a salt thereof:



(III-a),

wherein:

R^6 is -CN, -OH, $-OR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^bR^c$, $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl,

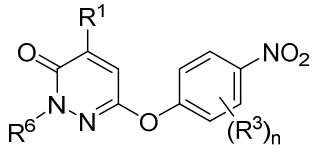
and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

X is as defined herein for formula (II).

[093] In some embodiments, each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl in R^6 is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

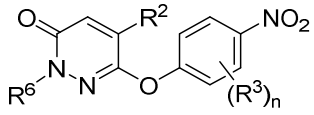
[094] In some embodiments, R^6 is C_1-C_6 alkyl.

[095] In some embodiments, the compound of formula (III-a) is a compound of formula (III-c):


(III-c)

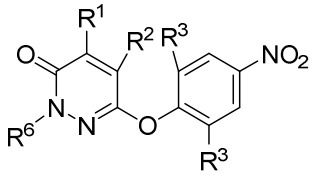
or a salt thereof, wherein R^1, R^3, R^6, and n are as described herein for formula (III-a).

[096] In some embodiments, the compound of formula (III-a) is a compound of formula (III-e):


(III-e)

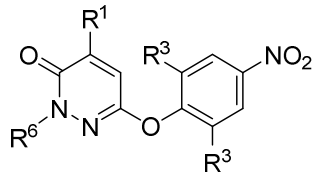
or a salt thereof, wherein R^2, R^3, R^6, and n are as described herein for formula (III-a).

[097] In some embodiments, the compound of formula (III-a) is a compound of formula (III-g):


(III-g)

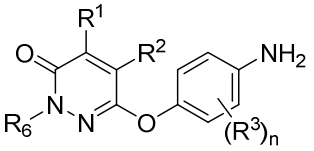
or a salt thereof, wherein R^1, R^2, R^3, and R^6 are as described herein for formula (III-a).

[098] In some embodiments, the compound of formula (III-a) is a compound of formula (III-i):


(III-i)

or a salt thereof, wherein R^1, R^3, and R^6 are as described herein for formula (III-a).

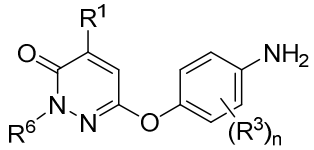
[099] In some embodiments, the method further comprises contacting the compound of formula (III-a) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV-a) or a salt thereof:


(IV-a).

[0100] In some embodiments, the second organic solvent used in the synthesis of the compound of formula (IV-a) can comprise DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a combination thereof. In some embodiments, the second organic solvent used in the synthesis of the compound of formula (IV-a) is DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, acetone, or a combination thereof. In some embodiments, the second organic solvent comprises THF. In some embodiments, the second organic solvent is THF.

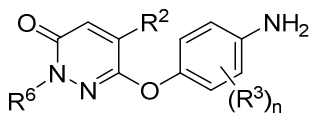
[0101] In some embodiments, the reducing agent used in the synthesis of the compound of formula (IV-a) can comprise H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride. In some embodiments, the reducing agent used in the synthesis of the compound of formula (IV-a) is H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride. In some embodiments, the reducing agent comprises H_2 gas and Pd/C. In some embodiments, the reducing agent is H_2 gas and Pd/C.

[0102] In some embodiments, the compound of formula (IV-a) is a compound of formula (IV-c):


(IV-c)

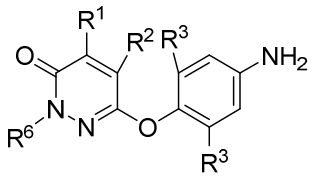
or a salt thereof, wherein R^1, R^3, R^6, and n are as described herein for formula (IV-a).

[0103] In some embodiments, the compound of formula (IV-a) is a compound of formula (IV-e):


(IV-e)

or a salt thereof, wherein R^2, R^3, R^6, and n are as described herein for formula (IV-a).

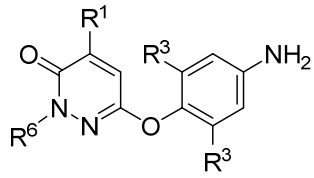
[0104] In some embodiments, the compound of formula (IV-a) is a compound of formula (IV-g):



(IV-g)

or a salt thereof, wherein R^1, R^2, R^3, and R^6 are as described herein for formula (IV-a).

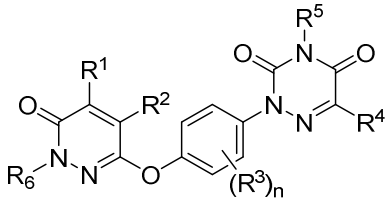
[0105] In some embodiments, the compound of formula (IV-a) is a compound of formula (IV-i):



(IV-i)

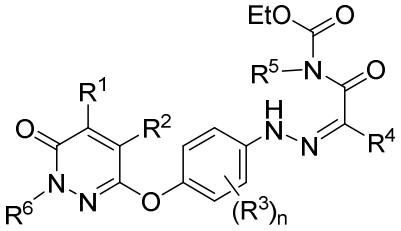
or a salt thereof, wherein R^1, R^3, and R^6 are as described herein for formula (IV-a).

[0106] In some embodiments, the method further comprises contacting the compound of formula (IV-a) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$, as described above, to form a compound of formula (V-a) or a salt thereof:



(V-a).

[0107] In some embodiments, prior to the formation of a compound of formula (V-a), the method comprises contacting a compound of formula (IV-a) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$, as described above, in the presence of an oxidizing agent and an acid to form a compound of formula (IV-a-int) or a salt thereof:



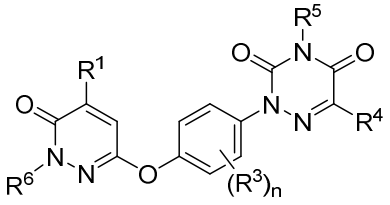
(IV-a-int).

[0108] In some embodiments, the oxidizing agent used in the synthesis of the compound of formula (IV-a-int) can comprise $NaNO_2$, KNO_2, or a combination thereof. In some embodiments, the oxidizing agent used in the synthesis of the compound of formula (IV-a-

int) is $NaNO_2$, KNO_2, or a combination thereof. In some embodiments, the acid used in the synthesis of the compound of formula (IV-a-int) can comprise HCl, AcOH, or a combination thereof. In some embodiments, the acid used in the synthesis of the compound of formula (IV-a-int) is HCl, AcOH, or a combination thereof.

[0109] In some embodiments, the method further comprises contacting the compound of formula (IV-a-int) with a base to form a compound of formula (V-a). In some embodiments, the base used in the synthesis of the compound of formula (V-a) can comprise NaOAc, KOAc, or a combination thereof. In some embodiments, the base used in the synthesis of the compound of formula (V-a) is NaOAc, KOAc, or a combination thereof.

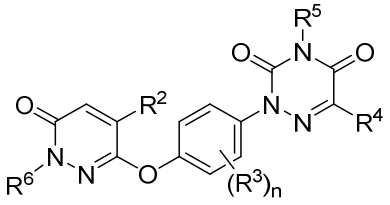
[0110] In some embodiments, the compound of formula (V-a) is a compound of formula (V-c):



(V-c)

or a salt thereof, wherein R^1, R^3, R^4, R^5, R^6, and n are as described herein for formula (V-a).

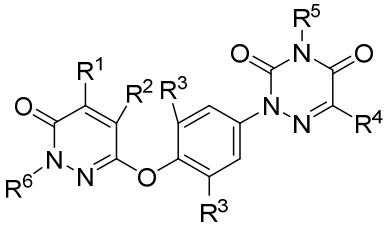
[0111] In some embodiments, the compound of formula (V-a) is a compound of formula (V-e):



(V-e)

or a salt thereof, wherein R^2, R^3, R^4, R^5, R^6, and n are as described herein for formula (V-a).

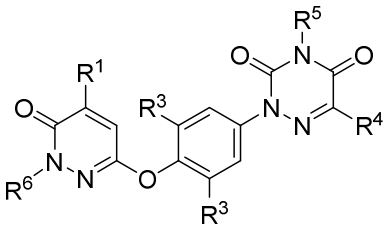
[0112] In some embodiments, the compound of formula (V-a) is a compound of formula (V-g):



(V-g)

or a salt thereof, wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein for formula (V-a).

[0113] In some embodiments, the compound of formula (V-a) is a compound of formula (V-i):



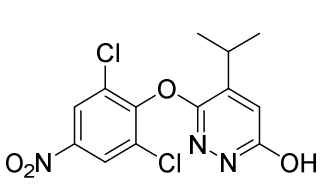
(V-i)

or a salt thereof, wherein R^1, R^3, R^4, R^5, and R^6 are as described herein for formula (V-a).

[0114] Embodiments of the compounds of formula (V) or (V-a) can be found in WO2019/240938, the contents of which are incorporated herein by reference.

[0115] In some embodiments, the compounds can be contacted at room temperature, above room temperature, or below room temperature. In some embodiments, the contacting occurs at room temperature.

[0116] In one aspect, the present disclosure provides a compound having the structure of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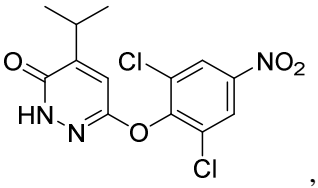
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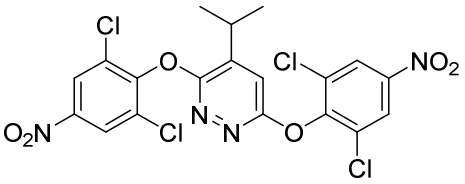
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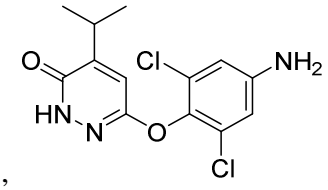
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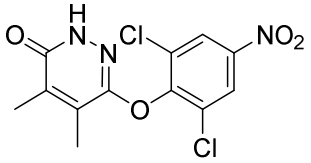
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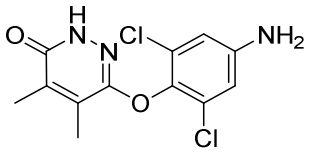
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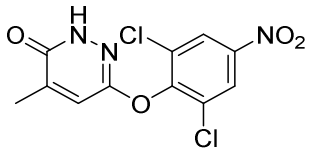
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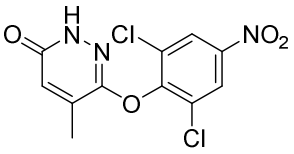
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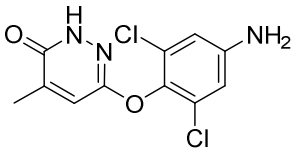
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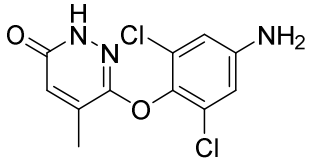
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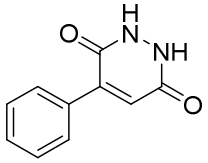
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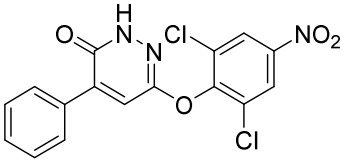
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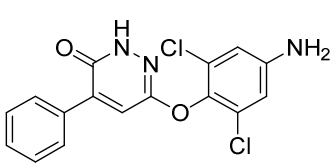
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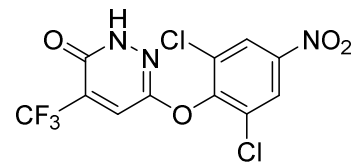
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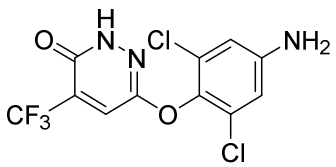
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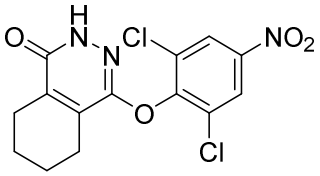
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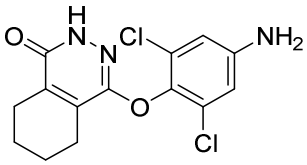
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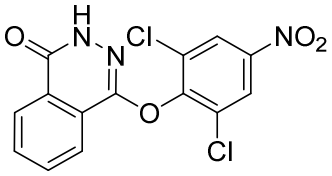
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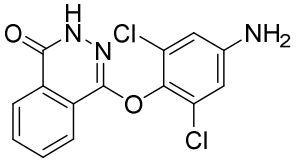
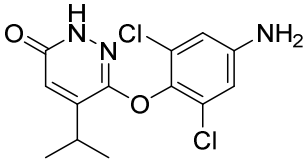

, or

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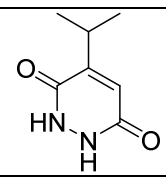
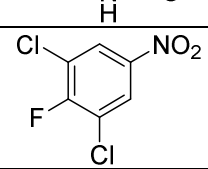
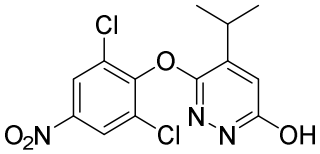
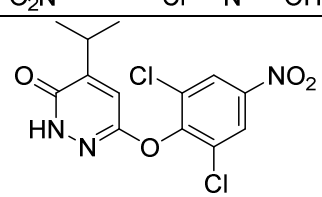
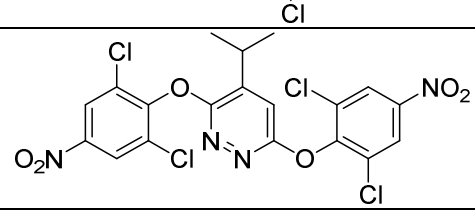
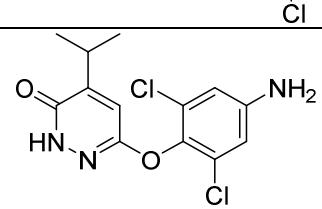
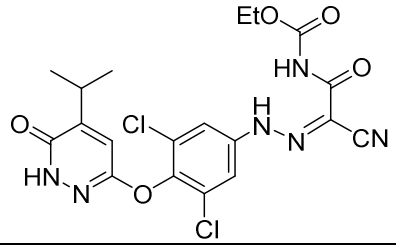
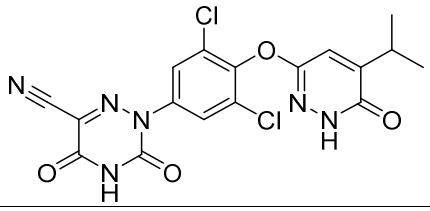
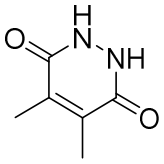
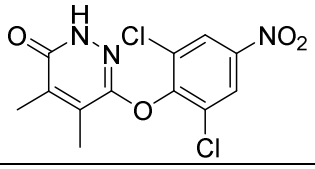
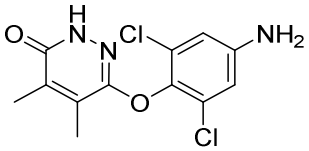
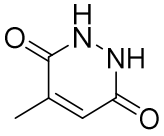
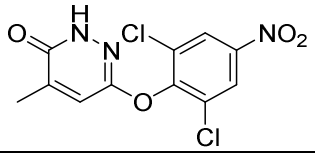
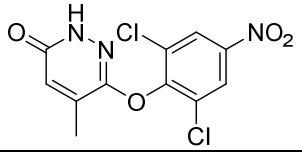
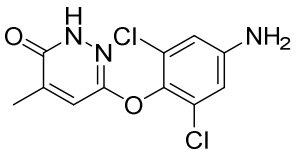
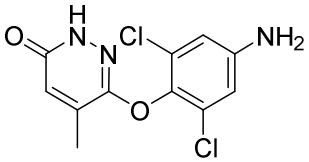
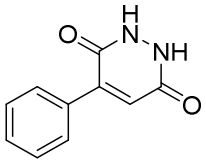
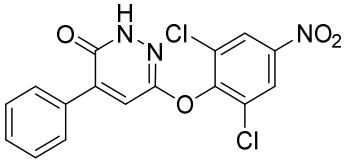
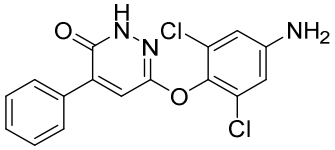
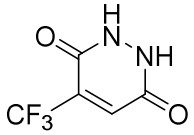
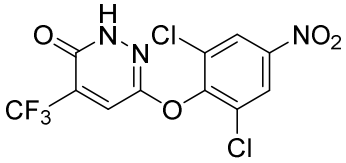
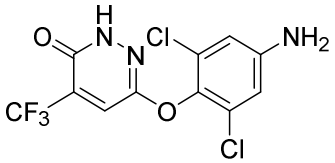
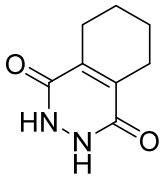
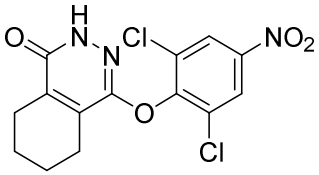
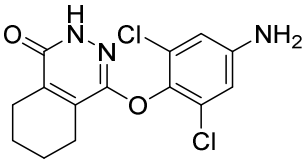
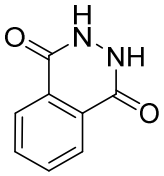
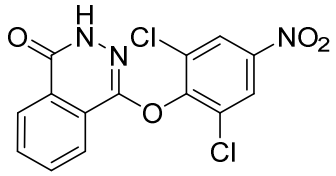
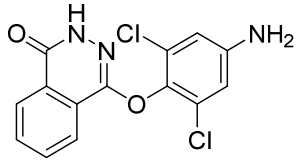
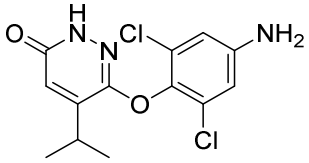
[0117] Examples of compounds of the present disclosure are shown in Table 1 below.

Table 1. Compounds of the Present Disclosure

Compound Number	Compound Structure
1-1	
1-2	
1-3	
1-4	
1-5	
Int. 7	

Int. 8	
MGL-3196	
2-1	
2-2	
2-3	
3-1	
3-2	
3-3	
3-4	
3-5	

4-1	
4-2	
4-3	
5-1	
5-2	
5-3	
6-1	
6-2	
6-3	
7-1	

7-2	
7-3	
8-1	

Pharmaceutically Acceptable Salts

[0118] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0119] In some embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0120] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-l,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-l,6-dioate, hydroxybenzoate, g-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, l-napthalenesulfonate, 2-napthalenesulfonate,

nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate, and xylenesulfonate.

[0121] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, l,2-ethanedisulfonic acid, 2- hydroxyethanesulfonic acid, benzenesulfonic acid, 2 -naphthalene sulfonic acid, 4-methylbicyclo- [2.2.2]oct-2-ene-l -carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-l- carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0122] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, N+(CI-4 alkyl)4, and the like.

[0123] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quatemization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quatemization.

Pharmaceutical Compositions and Methods of Treatment

[0124] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound or compounds of formula (V) or (V-a) or a salt thereof as an active ingredient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound or compounds of formula (V) or (V-a), or pharmaceutically acceptable salts or solvates thereof, and one or more pharmaceutically acceptable carriers or excipients.

[0125] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound or compounds of formula (V) or (V-a) or a salt thereof being prepared by a method described herein, and one or more pharmaceutically acceptable carriers or excipients.

[0126] The pharmaceutical compositions of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0127] In some embodiments, the pharmaceutical composition is formulated in a gel.

[0128] In some embodiments, the pharmaceutical composition is formulated in a tablet.

[0129] In some embodiments, the pharmaceutical composition is formulated in a pill.

[0130] In some embodiments, the pharmaceutical composition is formulated in a capsule.

[0131] In some embodiments, the pharmaceutical composition is formulated in a solution.

[0132] In some aspects, the present disclosure pertains, at least in part, to a method for treating a liver disease or disorder or a lipid disease or disorder by administering to a subject in need thereof a compound of formula (V) or (V-a) or a salt thereof.

[0133] In some embodiments, the liver disease or disorder treated by the methods of the invention is fatty liver disease.

[0134] In some embodiments, the liver disease or disorder treated by the methods of the invention is nonalcoholic fatty liver disease (NAFLD). In some embodiments, the liver disease or disorder treated by the methods of the invention is NASH.

[0135] In some embodiments, the lipid disease or disorder treated by the methods of the invention is selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL. In some embodiments,

the hypercholesterolemia is heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH).

[0136] In some embodiments, the subject has a risk for developing the liver disease or disorder described herein. In some embodiments, the subject has a risk for developing the lipid disease or disorder described herein.

[0137] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

DEFINITIONS

[0138] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description is intended to describe particular embodiments only, and is not intended to limit the scope of the invention.

[0139] Where a range of values is provided, it is understood that the range includes both of the endpoints with that range, as well as all intervening values.

[0140] The articles "a" and "an" as used herein and in the appended claims are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly indicates otherwise. By way of example, "an ultrapure form" means one ultrapure form or more than one ultrapure form.

[0141] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both". Other elements may optionally be present other than the elements specifically identified by the "and/or" clause. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements).

[0142] Unless explicitly indicated otherwise, the terms “approximately” and “about” are synonymous. In some embodiments, “approximately” and “about” refer to the recited amount, value, dose or duration ± 10%, ± 8%, ± 6%, ± 5%, ± 4%, ± 2%, ± 1%, or ± 0.5%. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration ± 5%. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration ± 2%. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration ± 1%.

[0143] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of' or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of."

[0144] As used herein, “alkyl”, “C_1, C_2, C_3, C_4, C_5 or C_6 alkyl” or “C_1-C_6 alkyl” is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl. In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0145] As used herein, the term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term “C_2-C_6” includes alkenyl groups containing two to six carbon atoms. The term “C_3-C_6” includes alkenyl groups containing three to six carbon atoms.

[0146] As used herein, the term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term “C_2-C_6” includes alkynyl groups containing two to six carbon atoms. The term “C_3-

C_6" includes alkynyl groups containing three to six carbon atoms. As used herein, "C_2-C_6 alkenylene linker" or "C_2-C_6 alkynylene linker" is intended to include C_2, C_3, C_4, C_5 or C_6 chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C_2-C_6 alkenylene linker is intended to include C_2, C_3, C_4, C_5 and C_6 alkenylene linker groups.

[0147] "Aminoalkyl" means an alkyl moiety as defined herein, substituted with one or more amino groups.

[0148] As used herein, the term "aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[0149] As used herein, the term "contact" or "contacting" refers an action causing two or more reactants to be in a proximity, e.g., such that the two or more reactants chemically react. In some embodiments, the contacting comprising mixing the two or more reactants. In some embodiments, the contacting is under a reaction condition suitable for forming the desired reaction product from the two or more reactants.

[0150] As used herein, the term "cycloalkyl" refers to a saturated or unsaturated nonaromatic hydrocarbon mono- or multi-ring (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C_3-C_{12}, C_3-C_{10}, or C_3-C_8). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl.

[0151] "Deuteroalkyl" refers to an alkyl group where one or more hydrogen atoms of an alkyl are replaced with deuterium.

[0152] As used herein, the term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[0153] "Haloalkyl" refers to an alkyl group where one or more hydrogen atoms of an alkyl are replaced with a halogen.

[0154] As used herein, the term "heterocycloalkyl" refers to a saturated or unsaturated nonaromatic 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*¸ 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group

consisting of nitrogen, oxygen and sulfur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidinyl, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like. In the case of multicyclic non-aromatic rings, only one of the rings needs to be non-aromatic (*e.g.*, 1,2,3,4-tetrahydronaphthalenyl or 2,3-dihydroindole).

[0155] As used herein, the term “heteroaryl” is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*¸ 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0156] “Hydroxyalkyl” means an alkyl moiety as defined herein, substituted with one or more hydroxy groups. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-

hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl.

[0157] It is understood that the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0158] As used herein, the term "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0159] As used herein, the term "subject" is interchangeable with the term "subject in need thereof," both of which refer to a subject having a disease or having an increased risk of developing the disease. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. In some embodiments, the mammal is a human.

[0160] As used herein, the term "tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerisation is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

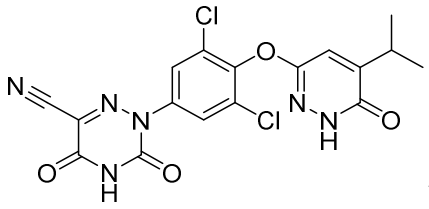
[0161] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0162] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[0163] As used herein, the term “salt” or “pharmaceutically acceptable salt” refers to a derivative of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc. Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3. It is to be understood that all

references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0164] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0165] As used herein, the term "MGL-3196" is equivalent 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 (i.e., ), or any of its pharmaceutically acceptable salts.

[0166] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

EXAMPLES

[0167] Unless otherwise specified, the analytical instruments and parameters used for compounds described in the Examples are as follows:

[0168] Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker NEO 600 MHz NMR spectrometer equipped with a 5 mm broadband observe probe. For ^{1}H NMR, 16 scans were co-added with a 90 degree pulse and a recycle delay of 10 seconds. For ^{13}C NMR, ^{13}C detection was accompanied with a ^{1}H composite pulse decoupling. Unless otherwise noted, 256 scans were co-added for ^{13}C NMR data collection. The chemical shift (δ) is reported in parts per million (ppm).

[0169] LC-MS chromatograms and spectra were recorded using a Shimadzu LCMS-2020 ultra high-speed mass spectrometer interfaced with a Shimadzu LC-2040C 3D liquid chromatography system.

[0170] The XRPD data were collected using a Rigaku X-ray generator: 30kV, 15 mA; Wavelength: K alpha 1, Goniometry: MiniFlex goniometer, Scan speed: 2.0000 °/min, Scan step: 0.02 °, Detector: Miniflex counter, Scan range: 3.0000 – 45.0000.

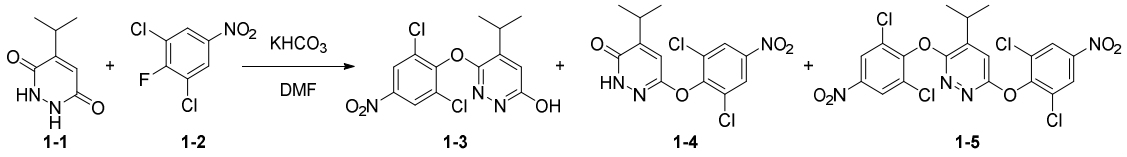
[0171] Melting points were acquired using a TA Instruments Inc. DSC Q200.

[0172] Abbreviations:

ACN and MeCN	acetonitrile
$CDCl_3$	chloroform-*d*
DCM	dichloromethane
DMF	N,N-dimethylformamide
g	gram(s)
HPLC	high performance liquid chromatography
mL	milliliter(s)
MHz	mega hertz
THF	tetrahydrofuran

Example 1: Synthesis of 6-(4-Amino-2,6-dichloro-phenoxy)-4-isopropyl-2H-pyridazin-3-one (Int. 7)

Synthesis of 6-(2,6-Dichloro-4-nitro-phenoxy)-4-isopropyl-2H-pyridazin-3-one (compound 1-4)



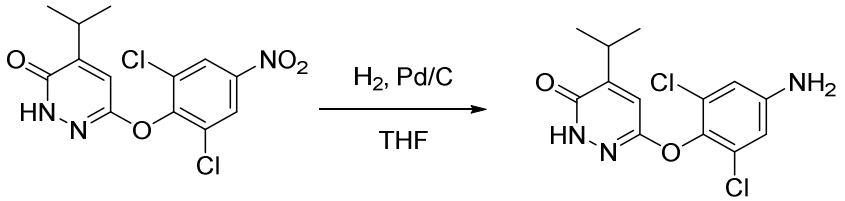
[0173] Potassium bicarbonate (2.34 g, 23.4 mmol) was added to the solution of compounds 3-1 (3.0 g, 19.5 mmol) and 3-2 (2.9 g, 13.6 mmol) in DMF (60 mL) and the mixture was stirred at room temperature for two hours before the reaction was quenched by water (180 mL). The resulting suspension was filtered. The filter cake was washed with water (60 mL) and dried under vacuum for 24 hours to afford crude compound 1-4 (4.93 g), which was further purified by slurry in ethyl acetate to afford compound 1-4 as an off-white solid (3.51 g, 74.9% purity). Compound 1-3, the regio-isomer of compound 1-4, was obtained by column chromatography purification.

[0174] Compound 1-4: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.16 (d, J = 0.8 Hz, 1H), 3.24 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.72, 154.89, 151.70, 150.85, 145.18, 130.55, 124.31, 119.65, 28.22, 20.75. LRMS for $C_{13}H_{12}Cl_2N_3O_4$ [M+H+] m/z = 344, $C_{13}H_{10}Cl_2N_3O_4$ [M+H-] m/z = 342. Crystalline solid of compound 1-4 was obtained from recrystallization in a solvent mixture of DCM and THF. Melting point: 270.82 °C. The peak values of the XRPD of compound 1-4 are listed below (PEAK: 21-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/0.6, Peak-Top=Summit).

2-Theta	d(A)
3.82	23.1098
4.079	21.6467
11.06	7.9932
14.68	6.0292
18.941	4.6814
20.12	4.4096
21.559	4.1184
21.96	4.0443
22.699	3.9142
24	3.7049
24.48	3.6333
24.8	3.5871
25.481	3.4928
26.559	3.3533
29.179	3.0579
31.28	2.8572
31.661	2.8237
32.781	2.7297
33.08	2.7057
34.538	2.5947
34.959	2.5645
35.42	2.5322
38.101	2.3599
39.98	2.2532
40.36	2.2329
41.901	2.1543
44.501	2.0343

[0175] Compound 1-3 (pure by HPLC): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.76 (s, 1H, NH), 8.27 (s, 2H), 6.84 (s, 1H), 3.16 (m, 1H), 1.34 (d, J = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.98, 151.08, 150.64, 147.85, 145.42, 130.64, 128.36, 124.50, 28.63, 21.19. LRMS for $C_{13}H_{12}Cl_2N_3O_4$ [M+H+] m/z = 344.

Synthesis of 6-(4-Amino-2,6-dichloro-phenoxy)-4-isopropyl-2H-pyridazin-3-one (Int. 7)

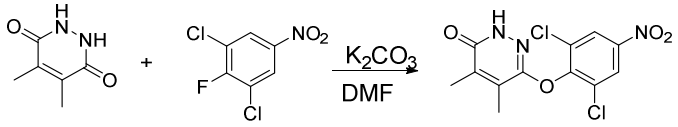


1-4 **Int. 7**

[0176] Palladium on carbon (5%, 50 mg) was added to the solution of compound 1-4 (0.5 g, 1.5 mmol) in THF (25 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford Int. 7 as an off-white solid (473 mg, 103.6%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.64 (s, 2H), 3.18 (m, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.53, 154.12, 152.89, 145.35, 137.15, 129.41, 120.44, 114.87, 28.29, 21.00. LRMS for $C_{13}H_{11}Cl_2N_3O_2$ [M+H-] m/z = 312.

Example 2. 6-(4-amino-2,6-dichlorophenoxy)-4,5-dimethylpyridazin-3(2H)-one (2-3)

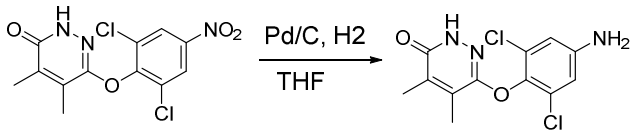
Synthesis of 6-(2,6-dichloro-4-nitrophenoxy)-4,5-dimethylpyridazin-3(2H)-one (2-2)



2-1 **1-2** **2-2**

[0177] Potassium carbonate (118 mg, 0.86 mmol) was added to the solution of 4,5-dimethyl-1,2-dihydropyridazine-3,6-dione (compound 2-1, 80 mg, 0.57 mmol) and compound 1-2 (84 mg, 0.40 mmol) in DMF (2.0 mL) and the mixture was stirred at room temperature for 3 hours before the reaction was quenched with water (6.0 mL). The resulting suspension was filtered. The filter cake was washed with water (2.0 mL) and dried under vacuum for 24 hours to afford crude compound 2-2 (114 mg), which was further purified by slurry in ethyl acetate to afford compound 2-2 as an off-white amorphous solid (93 mg, yield: 49.5%). Compound 2-2: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.72 (s, 1H, NH), 8.31 (s, 2H), 2.38 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.71, 151.52, 151.27, 145.28, 140.78, 133.08, 130.66, 124.47, 13.36, 13.00. LRMS for $C_{13}H_{10}Cl_2N_3O_4$ [M+H$^+$] m/z = 330.

Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4,5-dimethylpyridazin-3(2H)-one (2-3)

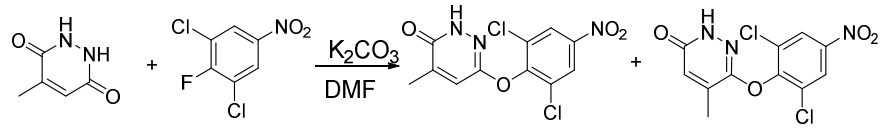


2-2 **2-3**

[0178] Palladium on carbon (5%, 3.0 mg) was added to the solution of compound 2-2 (30 mg, 0.09 mmol) in THF (2.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 2-3 as an off-white solid (32 mg, 116%). Compound 2-3: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (s, 2H), 2.34 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.28, 153.70, 148.80, 140.39, 137.37, 135.21, 130.01, 115.16, 13.25, 12.65. LRMS for $C_{12}H_{12}Cl_2N_3O_2$ [M+H$^+$] m/z = 300.

Example 3. Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-methylpyridazin-3(2H)-one (3-4) and 6-(4-amino-2,6-dichlorophenoxy)-5-methylpyridazin-3(2H)-one (3-5)

6-(2,6-dichloro-4-nitrophenoxy)-4-methylpyridazin-3(2H)-one (3-2) and 6-(2,6-dichloro-4-nitrophenoxy)-5-methylpyridazin-3(2H)-one (3-3)

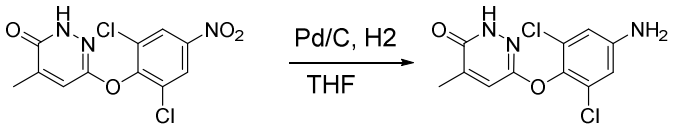


3-1 **1-2** **3-2** **3-3**

[0179] Potassium carbonate (329 mg, 2.38 mmol) was added to the solution of 4-methyl-1,2-dihydropyridazine-3,6-dione (compound 3-1, 200 mg, 1.59 mmol) and compound 1-2 (233 mg, 1.11 mmol) in DMF (4.0 mL) and the mixture was stirred at room temperature for 3 hours before the reaction was quenched with water (12.0 mL). The resulting suspension was filtered. The filter cake was washed with water (4.0 mL) and dried under vacuum for 24 hours to afford crude compound 3-2/3-3 (310 mg). Further purification by column chromatography gave off-white crystalline solid compound 3-2 (139 mg, yield: 27.8%) and off-white amorphous solid 3-3 (74 mg, yield: 14.8%). Compound 3-2: ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.29 (s, 1H, NH), 8.51 (s, 2H), 7.60 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$,) δ 160.50, 150.44, 150.12, 145.35, 145.33, 129.31, 124.67, 122.37, 16.24. LRMS for $C_{11}H_8Cl_2N_3O_2$ [M+H$^+$] m/z = 316. Compound 3-3: ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.23 (s, 1H, NH), 8.53 (s, 2H), 6.99 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ

160.07, 150.45, 150.29, 145.36, 136.98, 131.82, 129.15, 124.67, 15.61. LRMS for $C_{11}H_8Cl_2N_3O_2$ [M+H$^+$] m/z = 316.

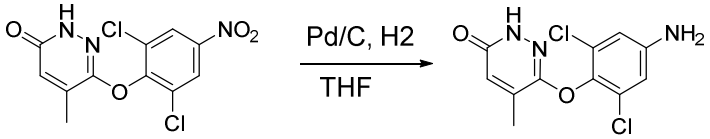
Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-methylpyridazin-3(2H)-one (3-4)



3-2 **3-4**

[0180] Palladium on carbon (5%, 2.5 mg) was added to the solution of compound 3-2 (25 mg, 0.08 mmol) in THF (2.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 3-4 as an off-white solid (21 mg, yield: 92.9%). Compound 3-4: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.11 (s, 1H, NH), 7.40 (s, 1H), 6.66 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 160.56, 151.37, 147.96, 144.14, 133.78, 127.*84*, 122.72, 112.88, 16.11. LRMS for $C_{11}H_{10}Cl_2N_3O_2$ [M+H+] m/z = 286.

Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-5-methylpyridazin-3(2H)-one (3-5)

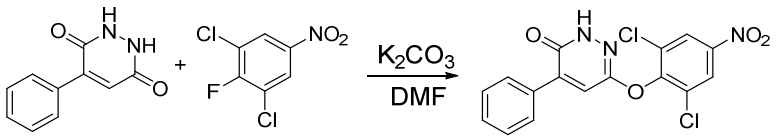


3-3 **3-5**

[0181] Palladium on carbon (5%, 1.5 mg) was added to the solution of compound 3-3 (15 mg, 0.05 mmol) in THF (5.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 3-5 as an off-white solid (16 mg, yield: 107%). Compound 3-5: ^{1}H NMR (600 MHz, CD_3OD) δ 6.89 (s, 1H), 6.70 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 163.52, 154.04, 148.90, 140.86, 137.19, 131.34, 129.90, 115.13, 16.60. LRMS for $C_{11}H_{10}Cl_2N_3O_2$ [M+H+] m/z = 286.

Example 4. Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-phenylpyridazin-3(2H)-one (4-3)

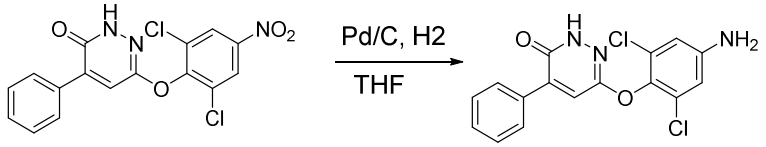
Synthesis of 6-(2,6-dichloro-4-nitrophenoxy)-4-phenylpyridazin-3(2H)-one (4-2)



4-1 **1-2** **4-2**

[0182] Potassium carbonate (249 mg, 1.80 mmol) was added to the solution of 4-phenyl-1,2-dihydropyridazine-3,6-dione (compound 4-1, 226 mg, 1.20 mmol) and compound 1-2 (177 mg, 0.84 mmol) in DMF (5.0 mL) and the mixture was stirred at room temperature for 3 hours before the reaction was quenched with water (20 mL). The resulting suspension was filtered. The filter cake was washed with water (5.0 mL) and dried under vacuum for 24 hours to afford crude compound 4-2 (177 mg), which was further purified by slurry in ethyl acetate to afford compound 4-2 as a light brown crystalline solid (110 mg, yield: 24.2%). Compound 4-2: ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.02 (s, 1H, NH), 8.27 (m, 2H), 7.84 (m, 2H), 7.48 (m 3H), 7.43 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.66, 152.04, 151.01, 145.45, 144.52, 132.91, 130.77, 128.94, 128.92, 128.82, 124.56, 122.07. LRMS for $C_{16}H_{10}Cl_2N_3O_2$ [M+H$^+$] m/z = 378.

Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-phenylpyridazin-3(2H)-one (4-3)

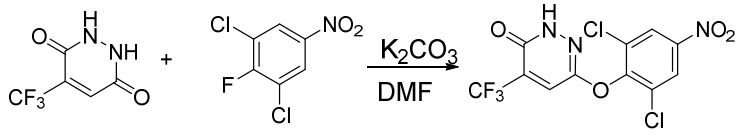


4-2 **4-3**

[0183] Palladium on carbon (5%, 3.0 mg) was added to the solution of compound 4-2 (30 mg, 0.08 mmol) in THF (2.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 4-3 as a light brown solid (23 mg, yield: 83.3%). Compound 4-3: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.85 – 7.84 (m, 2H), 7.56 (s, 1H), 7.50-7.48 (m, 3H), 6.71 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 152.41, 145.26, 139.33, 135.14, 127.44, 125.18, 121.47, 120.54, 120.21, 119.99, 114.46, 105.52. LRMS for $C_{16}H_{12}C_{l2}N_3O_2$ [M+H+] m/z = 348.

Example 5. Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-(trifluoromethyl)pyridazin-3(2H)-one (5-3)

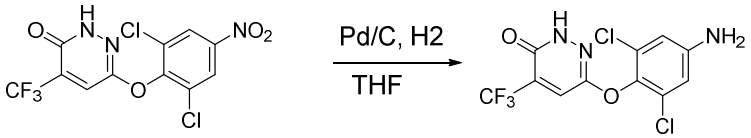
Synthesis of 6-(2,6-dichloro-4-nitrophenoxy)-4-(trifluoromethyl)pyridazin-3(2H)-one (5-2)



5-1 1-2 5-2

[0184] Sodium bicarbonate (46.7 mg, 0.56 mmol) was added to the solution of 4-(trifluoromethyl)-1,2-dihydropyridazine-3,6-dione (compound 5-1, 100 mg, 0.56 mmol) and compound 1-2 (58.3 mg, 0.28 mmol) in DMF (2.0 mL) below 5.0 °C, and the mixture was stirred at room temperature for 4 days before the reaction was quenched with water (6.0 mL). The resulting suspension was filtered. The filter cake was washed with water (2.0 mL) and dried under vacuum for 24 hours to afford crude compound 5-2 (109 mg), which was further purified by slurry in ethyl acetate to afford compound 5-2 as an off-white solid (58 mg, yield: 28.3%). Compound 5-2: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.11 (s, 1H, NH), 8.55 (s, 2H), 8.38 (s, 1H). LRMS for $C_{11}H_5Cl_2F_3N_3O_4$ [M+H$^+$] m/z = 370).

Synthesis of 6-(4-amino-2,6-dichlorophenoxy)-4-(trifluoromethyl)pyridazin-3(2H)-one (5-3)

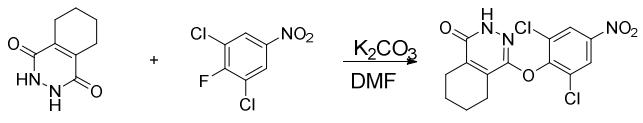


5-2 5-3

[0185] Palladium on carbon (5%, 1.5 mg) was added to the solution of compound 5-2 (15 mg, 0.04 mmol) in THF (2.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness. Compound 5-3 was obtained as an off-white solid after column chromatography purification (6.1 mg, yield: 44.3%). Compound 5-3: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (s, 1H, NH), 7.60 (s, 1H), 6.63 (s, 2H). LRMS for $C_{11}H_7Cl_2F_3N_3O_2$ [M+H$^+$] m/z = 340.

Example 6. Synthesis of 4-(4-amino-2,6-dichlorophenoxy)-5,6,7,8-tetrahydrophthalazin-1(2H)-one (6-3)

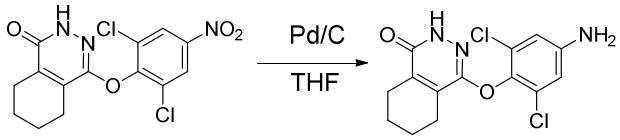
Synthesis of 4-(2,6-dichloro-4-nitrophenoxy)-5,6,7,8-tetrahydrophthalazin-1(2H)-one (6-2)



6-1 1-2 6-2

[0186] Potassium carbonate (699 mg, 5.05 mmol) was added to the solution of 2,3,5,6,7,8-hexahydrophthalazine-1,4-dione (compound 6-1, 560 mg, 3.37 mmol) and compound 1-2 (495 mg, 2.36 mmol) in DMF (5.0 mL) and the mixture was stirred at room temperature for 3 hours before the reaction was quenched with water (20 mL). The resulting suspension was filtered. The filter cake was washed with water (5.0 mL) and dried under vacuum for 24 hours to afford crude compound 6-2 (821 mg), which was further purified by slurry in ethyl acetate to afford compound 6-2 as a white solid (722 mg, yield: 60.2%). Compound 6-2: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.15 (s, 1H, NH), 8.51 (s, 2H), 2.65 (t, J = 5.8 Hz, 2H), 2.44 (t, J = 5.8 Hz, 2H), 1.81 – 1.70 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.90, 150.59, 149.67, 145.28, 141.37, 132.70, 129.28, 124.61, 23.03, 22.53, 20.26, 20.13. LRMS for $C_{14}H_{12}Cl_2N_3O_4$ [M+H$^+$] m/z = 356.

Synthesis of 4-(4-amino-2,6-dichlorophenoxy)-5,6,7,8-tetrahydrophthalazin-1(2H)-one (6-3)

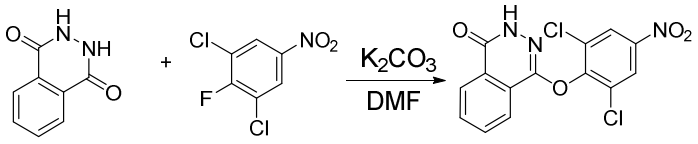


6-2 **6-3**

[0187] Palladium on carbon (5%, 2.5 mg) was added to the solution of compound 6-2 (25 mg, 0.07 mmol) in THF (2.0 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 6-3 as an off-white solid (20 mg, yield: 87.3%). Compound 6-3: ^{1}H NMR (600 MHz, CD_3OD) δ 6.70 (s, 2H), 2.73 (t, J = 4.9 Hz, 2H), 2.54 (t, J = 4.9 Hz, 2H), 1.88 – 1.78 (m, 4H). ^{13}C NMR (151 MHz, CD_3OD) δ 163.02, 153.43, 148.52, 141.45, 137.42, 136.55, 130.03, 115.30, 31.04, 24.38, 22.03, 21.91. LRMS for $C_{14}H_{14}Cl_2N_3O_2$ [M+H$^+$] m/z = 326.

Example 7. Synthesis of 4-(4-amino-2,6-dichlorophenoxy)phthalazin-1(2H)-one (7-3)

Synthesis of 4-(2,6-dichloro-4-nitrophenoxy)phthalazin-1(2H)-one (7-2)

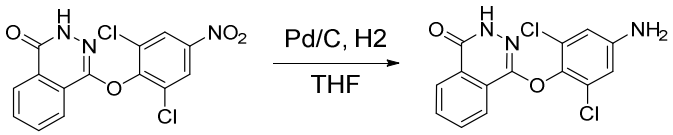


7-1 **1-2** **7-2**

[0188] Potassium carbonate (2.60 g, 18.50 mmol) was added to the solution of phthalic hydrazide (compound 7-1, 2.00 g, 12.33 mmol) and compound 1-2 (1.81 g, 8.63 mmol) in

DMF (20 mL) and the mixture was stirred at room temperature for 3 hours before the reaction was quenched with water (60 mL). The resulting suspension was filtered. The filter cake was washed with water (20 mL) and dried under vacuum for 24 hours to afford crude compound 7-2(2.98 g), which was further purified by slurry in ethyl acetate to afford compound 7-2 as an off-white solid (2.2 g, yield: 50.7%). Compound 7-2: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.09 (s, 1H, NH), 8.55 (s, 2H), 8.32 (d, J = 7.5 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.12 – 8.07 (m, 1H), 8.06 – 8.00 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.89, 150.39, 147.70, 145.43, 134.33, 133.40, 129.40, 129.09, 126.70, 124.63, 123.34, 122.77. LRMS for $C_{14}H_8Cl_2N_3O_4$ [M+H$^+$] m/z = 352.

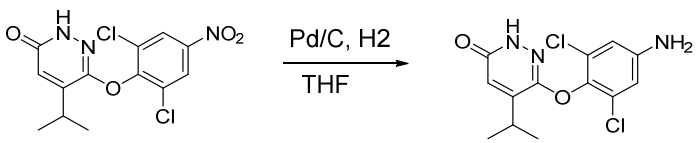
Synthesis of 4-(4-amino-2,6-dichlorophenoxy)phthalazin-1(2H)-one (7-3)



7-2 **7-3**

[0189] Palladium on carbon (5%, 10 mg) was added to the solution of compound 7-2 (100 mg, 0.28 mmol) in THF (10 mL). The solution was purged with nitrogen twice and then stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 7-3 as a light brown solid (98 mg, yield: 107%). Compound 7-3:^{1}H NMR (600 MHz, DMSO-d_6) δ 11.86 (s, 1H, NH), 8.28 (d, J = 7.7 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.05 – 8.01 (m, 1H), 8.00 – 7.95 (m, 1H), 6.71 (s, 2H), 5.64 (s, 2H, NH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.88, 148.48, 148.03, 134.00, 133.90, 132.85, 128.88, 127.90, 126.46, 123.40, 123.37, 112.92. LRMS for $C_{14}H_{10}Cl_2N_3O_2$ [M+H$^+$] m/z = 322.

Example 8. Synthesis of 6-(4-Amino-2,6-dichloro-phenoxy)-4-isopropyl-2H-pyridazin-3-one (8-1)



1-3 **8-1**

[0190] Palladium on carbon (5%, 45 mg) was added to the solution of compound 1-3 (450 mg, 1.31 mmol) in THF (25 mL). The solution was purged with nitrogen twice and then

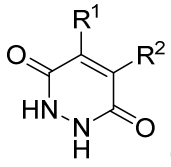
stirred under hydrogen atmosphere at room temperature for 5 hours. The mixture was filtered through a celite pad and the filtrate was concentrated to dryness to afford compound 8-1 as an off-white solid (410 mg, 99.8%). Compound 8-1: ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.08 (s, NH), 6.79 (s, 1H), 6.68 (s, 2H), 3.05 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.92, 150.65, 148.46, 146.69, 134.17, 128.21, 128.02, 113.41, 28.24, 21.16. LRMS for $C_{13}H_{13}Cl_2N_3O_2$ [$M+H^+$] m/z = 314.

EQUIVALENTS

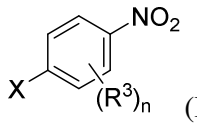
[0191] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

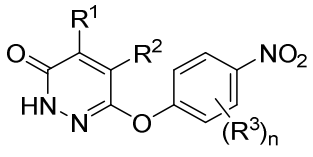
1. A method comprising contacting a compound of formula (I), a tautomer or a salt thereof:


(I)

with a compound of formula (II) or a salt thereof:


(II)

in a first organic solvent in the presence of a base, to form a compound of formula (III) or a salt thereof:


(III),

wherein:

R^1 and R^2 are each independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_4-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^1 and R^2 come together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^3 is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen,

-CN, -OH, -OR^a, -NR^bR^c, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^bR^c, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^a is independently C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6alkyl, or C_1-C_6 haloalkyl;

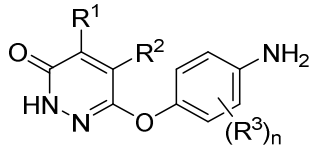
each R^b is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^c is independently hydrogen, deuterium, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -NH_2, -C(=O)CH_3, -C(=O)OH, -C(=O)OCH_3, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

X is halogen; and

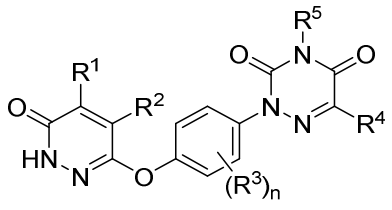
n is 0, 1, 2, 3, or 4.

2. The method of claim 1, further comprising contacting the compound of formula (III) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV) or a salt thereof:



(IV).

3. The method of claim 2, further comprising contacting the compound of formula (IV) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ to form a compound of formula (V) or a salt thereof:



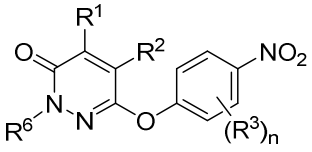
(V),

wherein:

R^4 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

4. The method of claim 1, further comprising contacting the compound of formula (III) or a salt thereof with R^6X to form a compound of formula (III-a) or a salt thereof:



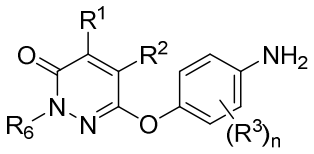
(III-a),

wherein:

R^6 is -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium,

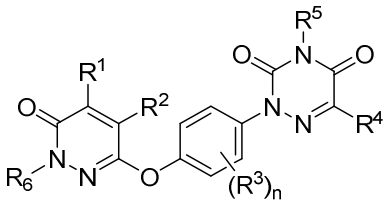
halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

5. The method of claim 4, further comprising contacting the compound of formula (III-a) or a salt thereof with a second organic solvent and a reducing agent to form a compound of formula (IV-a) or a salt thereof:



(IV-a).

6. The method of claim 5, further comprising contacting the compound of formula (IV-a) or a salt thereof with $R^4CH_2C(O)N(R^5)C(O)OCH_2CH_3$ to form a compound of formula (V-a) or a salt thereof:



(V-a)

wherein:

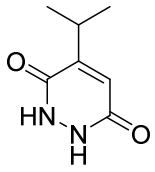
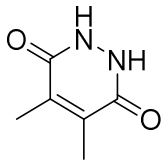
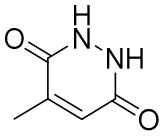
R^4 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -NO_2, -NR^bR^c, -$NHS(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$OC(=O)OR^b$, -$C(=O)NR^bR^c$, -$OC(=O)NR^bR^c$, -$NR^bC(=O)NR^bR^c$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

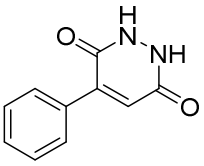
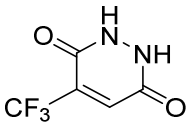
R^5 is hydrogen, halogen, -CN, -OH, -OR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^bR^c$, -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OR^a, -NR^bR^c, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^bR^c$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

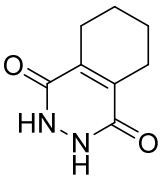
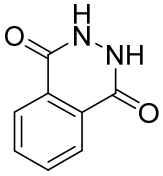
7. The method of claim 1, wherein X is F.

8. The method of claim 1, wherein R^3 is Cl.

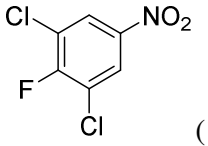
9. The method of claim 1, wherein the compound of formula (I) is compound 1-1, compound 2-1, compound 3-1, compound 4-1, compound 5-1, compound 6-1, or compound 7-1:

 (compound 1-1),  (compound 2-1),  (compound 3-1),

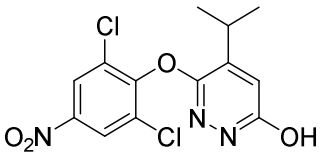
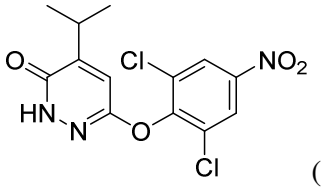
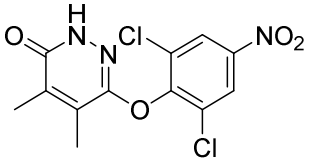
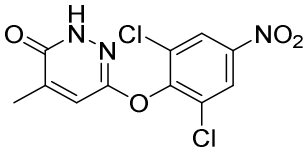
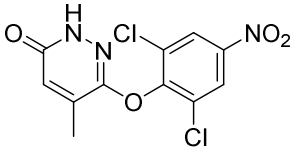
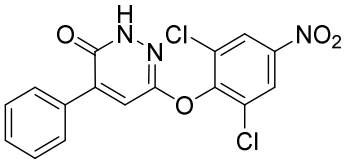
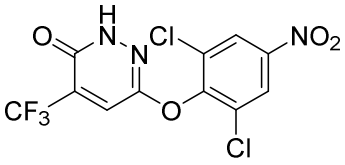
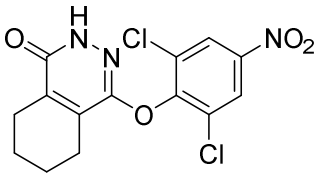
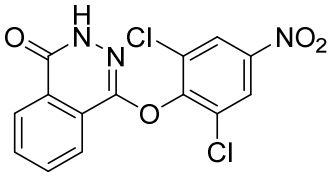
 (compound 4-1),  (compound 5-1),

 (compound 6-1), or  (compound 7-1).

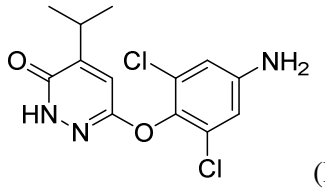
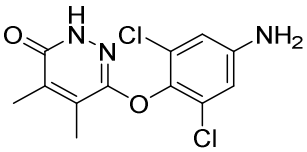
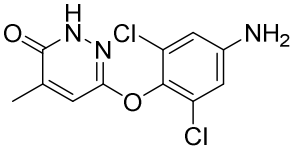
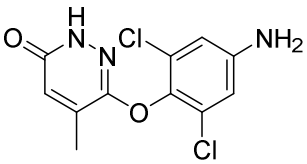
10. The method of claim 1, wherein the compound of formula (II) is compound 1-2:

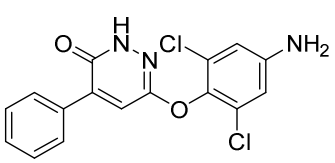
 (1-2).

11. The method of claim 1, wherein the compound of formula (III) is compound 1-3, compound 1-4, compound 2-2, compound 3-2, compound 3-3, compound 4-2, compound 5-2, compound 6-2, or compound 7-2:

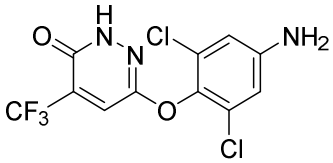

(compound 1-3),

(1-4),

(compound 2-2),

(compound 3-2),

(compound 3-3),

(compound 4-2),

(compound 5-2),

(compound 6-2), or

(compound 7-2).

12. The method of claim 2, wherein the compound of formula (IV) or the salt thereof is Int. 7, compound 2-3, compound 3-4, compound 3-5, compound 4-3, compound 5-3, compound 6-3, compound 7-3, or compound 8-1:

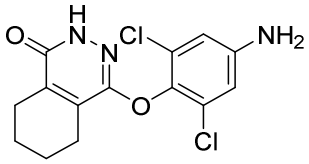

(Int. 7) ,

(compound 2-3),

(compound 3-4),

(compound 3-5),



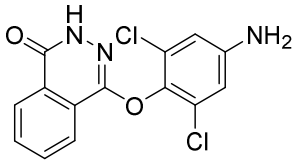
(compound 4-3),



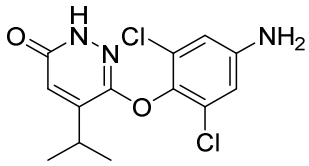
(compound 5-3),



(compound 6-3),



(compound 7-3), or



(compound 8-1).

13. The method of claim 1, wherein the first organic solvent comprises DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, or acetone.

14. The method of claim 1, wherein the base comprises $KHCO_3$ or K_2CO_3.

15. The method of claim 1, wherein the first organic solvent comprises THF.

16. The method of claim 2 or 5, wherein the reducing agent comprises H_2 gas and Pd/C, H_2 gas and Raney® nickel, H_2 gas and platinum (IV) oxide, ferrous chloride, or stannous chloride.

17. The method of claim 16, wherein the reducing agent comprises H_2 gas and Pd/C.

18. The method of claim 1, wherein the contacting occurs at room temperature.

19. The method of claim 1, wherein the contacting occurs above room temperature.

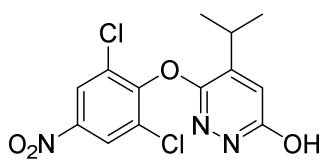
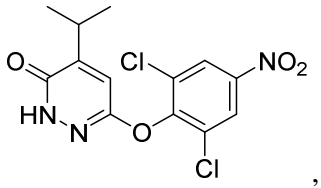
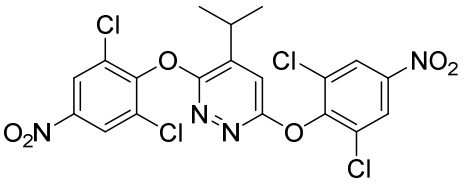
20. The method of claim 2 or 5, wherein the contacting occurs at room temperature.

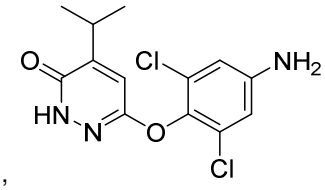
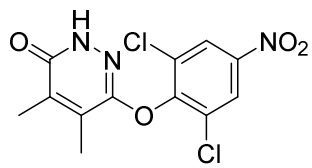
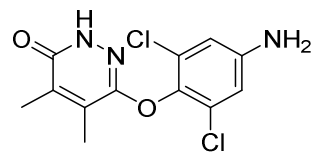
21. The method of claim 2 or 5, wherein the contacting occurs above room temperature.

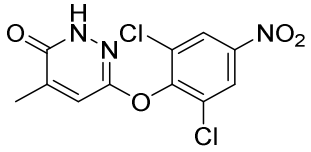
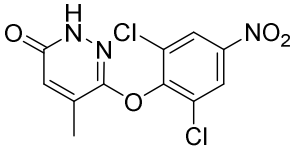
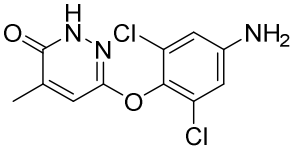
22. The method of claim 3, wherein the compound of formula (V) is 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (MGL-3196).

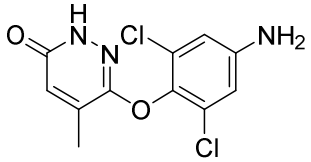
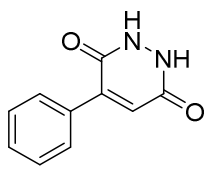
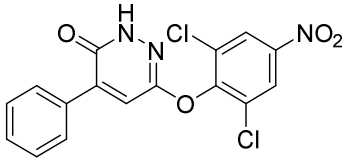
23. The method of claim 5, wherein the second organic solvent comprises DMF, DMAC, DMSO, acetonitrile, THF, DCM, dioxane, or acetone.

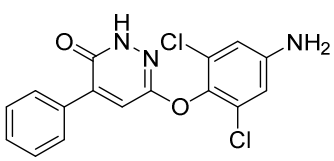
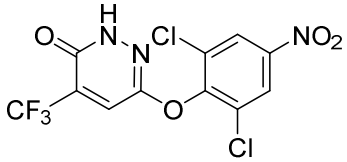
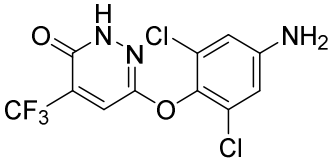
24. A compound having the structure of

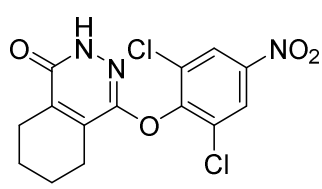
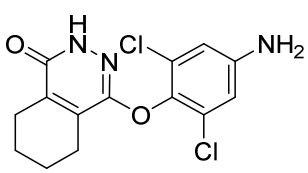
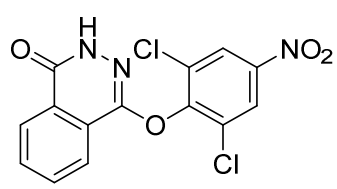
 ,  ,  ,

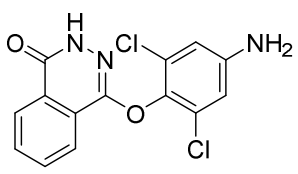
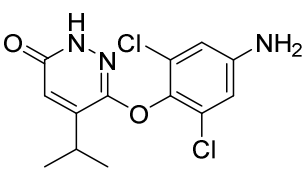
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 , or  .