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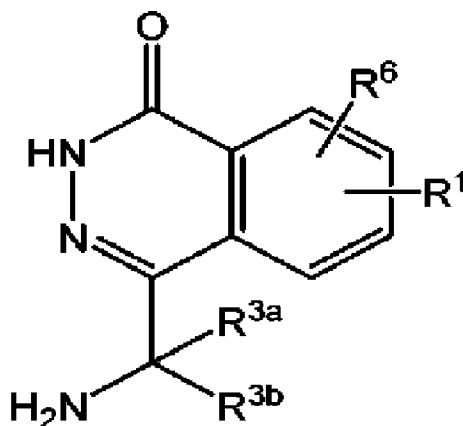
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(54) Titre : INHIBITEURS DE PRMT5 A COOPERATION AVEC LA MTA
(54) Title: MTA-COOPERATIVE PRMT5 INHIBITORS



Formula (I)

(57) **Abrégé/Abstract:**

The present invention relates to compounds that inhibit Protein Arginine N-Methyl Transferase 5 (PRMT5) activity. In particular, the present invention relates to compounds, pharmaceutical compositions and methods of use, such as methods of treating cancer using the compounds and pharmaceutical compositions of the present invention.

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Abstract:

The present invention relates to compounds that inhibit Protein Arginine N-Methyl Transferase 5 (PRMT5) activity. In particular, the present invention relates to compounds, pharmaceutical compositions and methods of use, such as methods of treating cancer using the compounds and pharmaceutical compositions of the present invention.

MTA-COOPERATIVE PRMT5 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 62/899,575, filed September 12, 2019, U.S. Provisional Application No. 62/942,833, filed December 3, 2019, U.S. Provisional Application No. 62/961,371, filed January 15, 2020, U.S. Provisional Application No. 62/994,927, filed March 26, 2020, and U.S. Provisional Application No. 63/060,261, filed August 3, 2020, the disclosure of each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds that are MTA-cooperative inhibitors of Protein Arginine N-Methyl Transferase 5 (PRMT5). In particular, the present invention relates to compounds, pharmaceutical compositions comprising the compounds and methods for use therefor.

BACKGROUND OF THE INVENTION

[0003] Protein Arginine N-Methyl Transferase (PRMT5) is a type II arginine methyltransferase that catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to an omega-nitrogen of the guanidino function of protein L-arginine residues (omega-monomethylation) and the transfer of a second methyl group to the other omega-nitrogen, yielding symmetric dimethylarginine (sDMA). PRMT5 forms a complex with MEP50 (methylosome protein 50), which is required for substrate recognition and orientation and is also required for PRMT5-catalyzed histone 2A and histone 4 methyltransferase activity (e.g., see Ho et al., (2013) PLOS ONE 8(8): 10.1371/annotation/e6b5348e-9052-44ab-8f06-90d01dc88fc2).

[0004] Homozygous deletions of p16/CDKN2a are prevalent in cancer and these mutations commonly involve the co-deletion of adjacent genes, including the gene encoding methylthioadenosine phosphorylase (MTAP). It is estimated that approximately 15% of all human cancers have a homozygous deletion of the MTAP gene (e.g., see Firestone & Schramm (2017) J. Am. Chem. Soc. 139(39):13754-13760. doi: 10.1021/jacs.7b05803. Epub 2017 Sep 20).

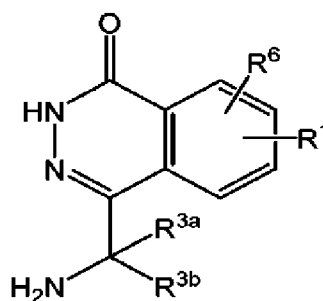
[0005] Cells lacking MTAP activity have elevated levels of the MTAP substrate, methylthioadenosine (MTA), which is a potent inhibitor of PRMT5. Inhibition of PRMT5 activity results in reduced methylation activity and increased sensitivity of cellular proliferation to PRMT5 depletion or loss of activity. Hence, the loss of MTAP activity reduces methylation activity of PRMT5 making the cells selectively dependent on PRMT5 activity.

SUMMARY OF THE INVENTION

[0006] Thus, we realized that MTA-cooperative inhibition of PRMT5 activity in MTAP deleted cancers will provide therapeutic benefit for a wide range of cancers. The compounds of the present invention provide this therapeutic benefit as MTA-cooperative inhibitors of PRMT5 that negatively modulate the activity of MTA-bound PRMT5 in a cell, particularly an MTAP-deficient cell, or for treating various forms of MTAP-associated cancer.

[0007] There is a need to develop new MTA-cooperative PRMT5 inhibitors that are capable of inhibiting PRMT5 activity in the presence of elevated MTA concentrations, particularly in MTAP-deficient cells.

[0008] In one aspect of the invention, compounds are provided that are represented by Formula (I):



Formula (I)

[0009] and pharmaceutically acceptable salts thereof:

[00010] wherein:

[0010] R¹ is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C1 – C5 alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC1-C3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the

heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R^2 ;

[0011] each Y is independently a bond or $-NR^4$;

[0012] each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2C1 - C3alkyl$, $-X-arC1-C3alkyl$, heteroalkyl, C2- C4 alkynyl, $-X-haloalkyl$, $-X-C1 - C5 alkyl$, $-Z-C1 - C5 alkyl$, heterocyclyl, $-X-L-cycloalkyl$, $-Z-cycloalkyl$, $-X-aryl$, $-Z-aryl$, or $-X-heteroaryl$, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5 ;

[0013] each X is independently a bond, O, S, $-NR^4$ - or $-NR^4C(O)-$

[0014] each Z is independently a bond, $-SO-$, $-SO_2-$, $-CH(OH)-$ or $-C(O)-$;

[0015] each L is independently a bond or C1 – C3 alkylene;

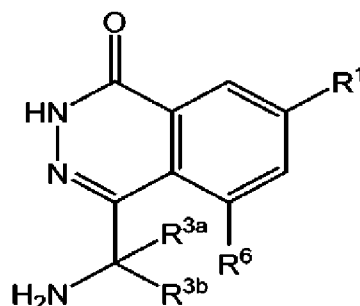
[0016] R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

[0017] each R^4 is independently hydrogen or C1 – C3 alkyl;

[0018] each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, $-X-haloalkyl$, $-Z-cycloalkyl$, $-X-arC1-C3alkyl$, $X-arC1-C3alkyl$ substituted with cyano $-X-L-cycloalkyl$, $-X-L-heteroaryl$ optionally substituted with one or more C1-C3alkyl or oxo, or $-X-aryl$; and

[0019] R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

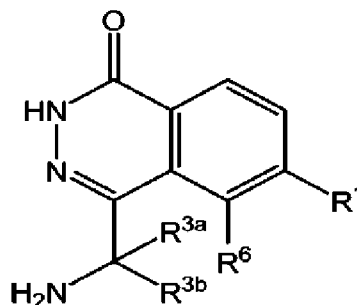
[0020] In one aspect of the invention, compounds are provided that are represented by Formula (I-A):



Formula (I-A)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z and L are as each defined for Formula I.

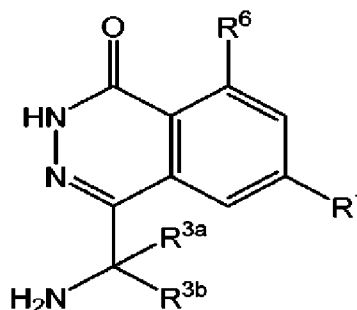
[0021] In one aspect of the invention, compounds are provided that are represented by Formula (I-B):



Formula (I-B)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z and L are as each defined for Formula I.

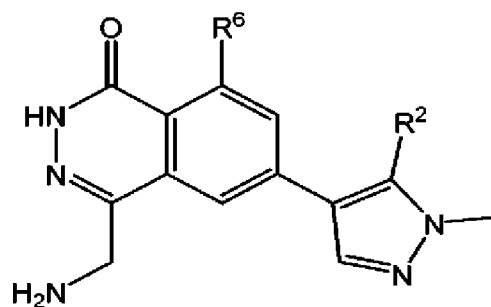
[0022] In one aspect of the invention, compounds are provided that are represented by Formula (I-C):



Formula (I-C)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z and L are as each defined for Formula I.

[0023] In another aspect of the invention, compounds are provided that are represented by Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

each Y is independently a bond or $-NR^4$ -;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2C1 - C3alkyl$, $-X-arC1-C3alkyl$, heteroalkyl, C2- C4 alkynyl, $-X-haloalkyl$, $-X-C1 - C5 alkyl$, $-Z-C1 - C5 alkyl$, heterocyclyl, $-X-L$ -cycloalkyl, $-Z-cycloalkyl$, $-X-aryl$, $-Z-aryl$, or $-X-heteroaryl$, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5 , or;

each X is independently a bond, O, S, $-NR^4$ - or $-NR^4C(O)$ -;

each Z is independently a bond, $-SO$ -, $-SO_2$ -, $-CH(OH)$ - or $-C(O)$ -;

each L is independently a bond or C1 – C3 alkylene;

each R^4 is independently hydrogen or C1 – C3 alkyl;

each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, $-X-haloalkyl$, $-Z-cycloalkyl$, $-X-arC1-C3alkyl$, $X-arC1-C3alkyl$ substituted with cyano, $-X-L-cycloalkyl$, $-X-L-heteroaryl$ optionally substituted with one or more C1-C3alkyl or oxo, or $-X-aryl$; and

R⁶ is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

[0024] In another aspect of the invention, intermediates are provided that are useful for the preparation of compounds of Formula (I), Formula (I-A), Formula (I-B) and Formula (I-C).

[0025] In another aspect of the invention, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0026] In yet another aspect of the invention, methods for inhibiting PRMT5 activity in a cell, comprising contacting the cell with a compound of Formula (I), Formula (I-A), Formula (I-B) and Formula (I-C). In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0027] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B), Formula (I-C) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. In one embodiment, the cell is an MTAP-deficient cell.

[0028] Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound or pharmaceutical composition of the present invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

[0029] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with MTAP double deletion (e.g., an MTAP-associated cancer); and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B), Formula (I-C) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0030] The present invention relates to MTA-cooperative PRMT5 inhibitors. In particular, the present invention relates to compounds that inhibit PRMT5 activity in the presence of bound MTA, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor.

DEFINITIONS

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference to the extent they are consistent with the present disclosure. Terms and ranges have their generally defined definition unless expressly defined otherwise.

[0032] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms may also be used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an “alkyl” moiety generally refers to a monovalent radical (e.g. $\text{CH}_3\text{-CH}_2\text{-}$), in certain circumstances a bivalent linking moiety can be “alkyl,” in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., $\text{-CH}_2\text{-CH}_2\text{-}$), which is equivalent to the term “alkylene.” (Similarly, in circumstances in which a divalent moiety is required and is stated as being “aryl,” those skilled in the art will understand that the term “aryl” refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S).

[0033] As used herein, “PRMT5” refers to a mammalian Protein Arginine N-Methyl Transferase 5 (PRMT5) enzyme.

[0034] As used herein, a “PRMT5 inhibitor” or “MTA-cooperative PRMT5 inhibitor” refers to compounds of the present invention that are represented by Formula (I) as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of the PRMT5 in the presence of bound MTA in vitro or in vivo, or in cells expressing elevated levels of MTA.

[0035] As used herein, “MTAP” refers to a mammalian methylthioadenosine phosphorylase (MTAP) enzyme.

[0036] An “MTAP-associated disease or disorder” as used herein refers to diseases or disorders associated with or mediated by or having a loss of MTAP activity resulting in sensitizing the disorder to selective inhibition of PRMT5 activity. A non-limiting example of an MTAP-associated disease or disorder is an MTAP-associated cancer.

[0037] The term "amino" refers to -NH_2 .

[0038] The term "acetyl" refers to -C(O)CH_3 .

[0039] As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent wherein the alkyl and aryl portions are as defined herein.

[0040] The term "alkyl" as employed herein refers to saturated straight and branched chain aliphatic groups having from 1 to 12 carbon atoms. As such, "alkyl" encompasses C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[0041] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms. As such, "alkenyl" encompasses C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Examples of alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0042] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms. As such, "alkynyl" encompasses C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} groups. Examples of alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0043] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Examples of alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Exemplary alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Exemplary alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0044] The term "alkoxy" refers to $\text{-OC}_1\text{ - C}_6$ alkyl.

[0045] The term "cycloalkyl" as employed herein is a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. As such, "cycloalkyl" includes C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} and C_{12} cyclic hydrocarbon groups. Examples of cycloalkyl groups

include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0046] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are independently replaced O, S, or NR^x, wherein R^x is hydrogen or C1 – C3 alkyl. Examples of heteroalkyl groups include methoxymethyl, methoxyethyl and methoxypropyl.

[0047] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings. As such, "aryl" includes C₆, C₁₀, C₁₃, and C₁₄ cyclic hydrocarbon groups. An exemplary aryl group is a C₆-C₁₀ aryl group. Particular aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aryl" group also includes fused multicyclic (*e.g.*, bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic, such as indenyl.

[0048] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group wherein the moiety is linked to another group via the alkyl moiety. An exemplary aralkyl group is –(C₁ – C₆)alkyl(C₆ – C₁₀)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. For example, an arC₁-C₃alkyl is an aryl group covalently linked to a C₁-C₃ alkyl.

[0049] A "heterocyclyl" or "heterocyclic" group is a mono- or bicyclic (fused or spiro) ring structure having from 3 to 12 atoms, (3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 atoms), for example 4 to 8 atoms, wherein one or more ring atoms are independently –C(O)–, N, NR⁴, O, or S, and the remainder of the ring atoms are quaternary or carbonyl carbons. Examples of heterocyclic groups include, without limitation, epoxy, oxiranyl, oxetanyl, azetidiny, aziridiny, THFyl, tetrahydropyranyl, tetrahydrothiophenyl, pyrrolidiny, piperidiny, piperaziny, imidazolidiny, thiazolidiny, thiatanyl, dithianyl, trithianyl, azathianyl, oxathianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinoliny, piperidonyl, 4-piperidonyl, thiomorpholiny, dimethyl-morpholiny, and morpholiny. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

[0050] As used herein, "L-heterocyclyl" refers to a heterocyclyl group covalently linked to another group via an alkylene linker

[0051] As used herein, the term "heteroaryl" refers to a group having 5 to 14 ring atoms, preferably 5, 6, 10, 13 or 14 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic

array; and having, in addition to carbon atoms, from one to three heteroatoms that are each independently N, O, or S. "Heteroaryl" also includes fused multicyclic (e.g., bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic and at least one ring contains an N, O, or S ring atom.

[0052] Examples of heteroaryl groups include acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolynyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, furanyl, furazanyl, imidazolynyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizynyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizynyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0053] A "L-heteroaralkyl" or "L-heteroarylalkyl" group comprises a heteroaryl group covalently linked to another group via an alkylene linker. Examples of heteroalkyl groups comprise a C₁-C₆ alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Examples of heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, thiazolylethyl, benzimidazolylmethyl, benzimidazolylethyl, quinazolinylmethyl, quinolinylmethyl, quinolinylethyl, benzofuranylmethyl, indolinylethyl, isoquinolinylmethyl, isoinodylemethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

[0054] An "arylene," "heteroarylene," or "heterocyclylene" group is a bivalent aryl, heteroaryl, or heterocyclyl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0055] As employed herein, when a moiety (e.g., cycloalkyl, aryl, heteroaryl, heterocyclyl, urea, etc.) is described as "optionally substituted" without expressly stating the substituents it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents.

[0056] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0057] The term "haloalkyl" refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Exemplary haloalkyls are trifluoromethyl, difluoromethyl, fluoro-chloromethyl, chloromethyl, and fluoromethyl.

[0058] The term "hydroxyalkyl" refers to -alkylene-OH.

[0059] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of PRMT5 enzyme.

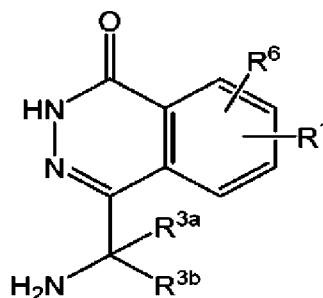
[0060] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of PRMT5. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0061] As used herein, "treatment" means any manner in which the symptoms or pathology of a condition, disorder or disease in a patient are ameliorated or otherwise beneficially altered.

[0062] As used herein, "amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition" refers to any lessening, whether permanent or temporary, lasting or transient, that can be attributed to or associated with administration of the composition.

COMPOUNDS

[0063] In one aspect of the invention, compounds are provided that are represented by Formula (I):



Formula (I)

[0064] or a pharmaceutically acceptable salt thereof:

[0065] wherein:

[0066] R¹ is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C1 – C5 alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC1-C3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R²;

[0067] each Y is a bond or -NR⁴-;

[0068] each R² is independently hydroxy, halogen, cyano, cyanomethyl, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵;

[0069] each X is independently a bond, O, S, -NR⁴- or -NR⁴C(O)-;

[0070] each Z is independently a bond, -SO-, -SO₂-, -CH(OH)- or -C(O)-;

[0071] each L is independently a bond or C1 – C3 alkylene;

[0072] R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

[0073] each R⁴ is independently hydrogen or C1 – C3 alkyl;

[0074] each R⁵ is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

[0075] R⁶ is hydrogen, halogen, haloalkyl, C1-C3 alkyl or alkoxy.

[0076] In one embodiment for compounds of Formula (I), R¹ is hydrogen.

[0077] In another embodiment for compounds of Formula (I), R¹ is halogen. In certain embodiments, the halogen is bromine.

[0078] In one embodiment for compounds of Formula (I), R¹ is -L-CN. In one embodiment, L is C1 – C3 alkylene. In certain embodiments, the C1 – C3 alkylene is methylene.

[0079] In one embodiment for compounds of Formula (I), R¹ is -Y-C1 – C5 alkyl. In one embodiment, Y is a bond and the C1 – C5 alkyl is methyl. In one embodiment, Y is -NR⁴- and the C1 – C5 alkyl is methyl, ethyl or propyl.

[0080] In one embodiment for compounds of Formula (I), R¹ is hydroxyalkyl.

[0081] In one embodiment for compounds of Formula (I), R¹ is -Y-heterocyclyl. In certain embodiments, Y is a bond and the heterocyclyl is azetidiny, THFyl or morpholinyl.

[0082] In one embodiment for compounds of Formula (I), R¹ is -Y-aryl wherein the aryl is optionally substituted with one or more R².

[0083] In certain embodiments, Y is a bond and the aryl is phenyl optionally substituted with one or two R². In one embodiment, the one or two R² groups are each independently C1 – C3 alkyl, cyano or halogen.

[0084] In one embodiment for compounds of Formula (I), R¹ is -Y-cycloalkyl. In one embodiment, Y is a bond and the cycloalkyl is cyclopentyl.

[0085] In one embodiment for compounds of Formula (I), R¹ is -Y-heteroaryl optionally substituted with one or more R². In certain embodiment, the heteroaryl is, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, triazolyl, oxidazolyl, pyridyl, pyridiazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl, pyrazolopyridinyl, 1*H*-pyrrolopyridyl, pyrazolopyrimidinyl, imidazopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4*λ*⁴-

imidazopyrimidinyl, 2*H*-4 λ^4 -imidazopyridazinyl, oxazolopyridyl or 5,6-dihydro-8*H*-imidazooxazinyl, each optionally substituted with one or more R². In one embodiment, Y is a bond.

[0086] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is azetidiny and R² is -(NR⁴)₂.

[0087] In one embodiment, R¹ is heteroaryl, Y is a bond and the heteroaryl is tetrahydropyrazolopyrazinyl, optionally substituted with one or more R². In one embodiment, the tetrahydropyrazolopyrazinyl is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-3-yl optionally substituted with one or more R². In one embodiment, the tetrahydropyrazolopyrazinyl is substituted with one R². In one embodiment, R² is -X-C1-C5 alkyl, arC1-C3alkyl, -Z-C1-C5 alkyl, -Z-cycloalkyl or -X-aryl. In one embodiment, R² is -Z-cycloalkyl, wherein Z is a bond and the cycloalkyl is cyclopropyl. In one embodiment, R² is -Z-cycloalkyl, wherein Z is -C(O)- and the cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclo[1.1.1]pentyl.

[0088] In one embodiment wherein R¹ is Y-heteroaryl, Y is a bond and the heteroaryl is pyrazolopyridinyl optionally substituted with one or more R². In one embodiment, the pyrazolylpyridinyl is substituted with one R², wherein the one R² is alkoxy or -X-aryl. In one embodiment, the alkoxy is methoxy or isopropoxy. In certain embodiments, the -X-aryl, the X is O and the aryl is phenyl.

[0089] In one embodiment, Y is a bond and the R¹ heteroaryl is pyridyl, optionally substituted with one or two R². In certain embodiments, the pyridyl is substituted with one R², wherein R² is hydroxy, halogen, cyano, cyanomethyl, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C1 - C3alkyl, arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 - C5 alkyl, -Z-C1 - C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵.

[0090] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-C1 - C5 alkyl, X is a bond and the C1 - C5 alkyl is methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl.

[0091] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-haloalkyl, X is a bond and the haloalkyl is difluoromethyl or trifluoromethyl. In

another embodiment, R² is -X-haloalkyl, wherein X is O, and wherein the haloalkyl is difluoromethyl or trifluoromethyl.

[0092] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-L-cycloalkyl, wherein X is a bond, L is a bond and the cycloalkyl is cyclopropyl or cyclohexyl. In another embodiment, R² is -X-L-cycloalkyl, wherein X is a bond, L is methylene and the cycloalkyl is cyclopropyl. In one embodiment, R² is -X-L-cycloalkyl, wherein X is O, L is methylene and the cycloalkyl is cyclopropyl.

[0093] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is C2-C4 alkynyl, wherein the alkynyl is ethynyl or prop-2-ynyl.

[0094] In another embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -SO₂C1 – C3 alkyl, wherein the C1 – C3 alkyl is methyl.

[0095] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is heterocyclyl, wherein the heterocyclyl is morpholinyl or tetrahydropyranyl.

[0096] In other embodiments, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-heteroaryl, wherein the heteroaryl is optionally substituted with one or more R⁵. In one embodiment, X is a bond, the heteroaryl is pyrazolyl substituted with one R⁵, wherein R⁵ is C1- C3 alkyl. In one embodiment, X is a bond, the heteroaryl is pyridyl or pyrimidinyl, each optionally substituted with one R⁵.

[0097] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is arC1-C3alkyl, wherein the arC1-C3alkyl is benzyl.

[0098] In one embodiment wherein R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-heteroaryl, wherein the X is O, and the heteroaryl is quinolinyl optionally substituted with one or more R⁵. In another embodiment, the X is -NR⁴-, and the heteroaryl is quinolinyl optionally substituted with one or more R⁵.

[0099] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-aryl, wherein X is O and the aryl is phenyl optionally substituted with one, two or three R⁵. In one embodiment, each of the one, two or three R⁵ groups is independently selected from the group consisting of cyano, halogen, C1 – C3 alkyl and alkoxy. In one embodiment, X is S and the aryl is phenyl optionally substituted with one R⁵, wherein R⁵ is halogen or C1-C3 alkyl. In one embodiment, X is O and the aryl is phenyl optionally

substituted with two R⁵ groups, wherein each R⁵ group is independently cyano. In one embodiment, X is -NR⁴- and the aryl is phenyl optionally substituted with two R⁵ groups, wherein each R⁵ group is independently alkoxy. In certain embodiments, each alkoxy is methoxy.

[0100] In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is halogen, wherein the halogen is chlorine or fluorine. In one embodiment, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl and R² is -X-L-cycloalkyl, heterocyclyl or -X-aryl, wherein the aryl is optionally substituted with one or more R⁵. In one embodiment, R² is -X-L-cycloalkyl, wherein X and L are each a bond and the cycloalkyl is cyclohexyl. In one embodiment, R² is heterocyclyl, wherein the heterocyclyl is tetrahydropyranyl. In one embodiment, R² is -X-aryl, wherein the aryl is phenyl substituted with two R⁵, wherein each R⁵ is cyano.

[0101] In certain embodiments, R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyridyl substituted with two R². In one embodiment, each R² is independently -X-C1 – C5 alkyl or one R² is halogen or cycloalkyl and the second R² is -X-C1 – C5 alkyl, wherein X is a bond.

[0102] In one embodiment for compounds of Formula (I), R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyrimidinyl, optionally substituted with one or two R². In one embodiment, the pyrimidinyl is substituted with one R², wherein R² is -X-C1 – C5 alkyl or -X-haloalkyl. In one embodiment, each X is a bond.

[0103] In one embodiment for compounds of Formula (I), R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is quinolinyl, optionally substituted with one or two R². In certain embodiments, the one R² group is cyano. In certain embodiments, one R² group is cyano and the second R² is halogen or -X-C1 C5 alkyl.

[0104] In one embodiment for compounds of Formula (I), R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is isothiazolyl, optionally substituted with one or two R². In one embodiment, R² is -X-aryl optionally substituted with one R⁵, wherein the aryl is naphthyl substituted with one R⁵, wherein R⁵ is cyano.

[0105] In one embodiment for compounds of Formula (I), R¹ is -Y-heteroaryl, Y is a bond and the heteroaryl is pyrazolyl, optionally substituted with one, two or three R² groups.

[0106] In certain embodiments, the pyrazolyl is substituted with one R^2 , wherein R^2 is cyano, -X-C1 – C5 alkyl, hydroxyalkyl, arC1-C3alkyl or -X-aryl, wherein the aryl is optionally substituted with one or more R^5 . In one embodiment, R^2 is -X-C1 – C5 alkyl, wherein X is a bond and the C1 – C5 alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl.

[0107] In other embodiments, the pyrazolyl is substituted with two R^2 groups, wherein the two R^2 groups are independently (1) -X-C1 – C5 alkyl, (2) -X-C1 – C5 alkyl and halogen, (3) -X-C1 – C5 alkyl and alkoxy, (4) -X-C1 – C5 alkyl and -N(R^4)₂, (5) X-C1 – C5 alkyl and -X-haloalkyl, (6) -X-C1 – C5 alkyl and arC1-C3alkyl, (7) -X-C1 – C5 alkyl and -X-L-cycloalkyl, (8) -X-C1 – C5 alkyl and -heterocyclyl, (9) -X-C1 – C5 alkyl and -X-aryl optionally substituted with one or more R^5 , (10) -X-C1 – C5 alkyl and -X-heteroaryl optionally substituted with one or more R^5 , (11) -X-C1 – C5 alkyl and cyanomethyl, (12) -X-C1 – C5 alkyl and cyano, (13) cyano and halogen, wherein the halogen is chlorine or fluorine, (14) cyano and -X-L-cycloalkyl, (15) independently halogen, (16) cyano and alkoxy, wherein each X is a bond, (17) cyano and -X-aryl, (18) cyano and -X-heteroaryl, (19) cyano and heterocyclyl (20) halogen and -X-arC1-C3alkyl or X-arC1-C3alkyl substituted with cyano, and (21) halogen and -X-aryl.

[0108] In one embodiment wherein R^1 is pyrazolyl, the pyrazolyl is substituted with two R^2 , wherein one R^2 is -X-C1 – C5 alkyl and the second R^2 is -X-aryl optionally substituted with one or more R^5 . In one embodiment, each X is a bond and the aryl is phenyl substituted with two R^5 , wherein (1) each R^5 is independently -X-C1 – C5 alkyl, wherein X is a bond; (2) one R^5 is cyano and one R^5 is -X-C1 – C5 alkyl, wherein X is a bond; (3) one R^5 is cyano and one R^5 is -X-L-cycloalkyl, wherein X is a bond and L is a bond, methylene or ethylene; (4) one R^5 is cyano and one R^5 is halogen; (5) one R^5 is cyano and one R^5 is alkoxy; (6) each R^5 is independently cyano or (7) each R^5 is independently halogen.

[0109] In one embodiment wherein R^1 is pyrazolyl, the pyrazolyl is substituted with two R^2 , wherein one R^2 is -X-C1 – C5 alkyl and the second R^2 is -X-aryl optionally substituted with one or more R^5 . In one embodiment, the X is a bond and the aryl is naphthyl substituted with one R^5 , wherein R^5 is cyano or halogen. In one embodiment, the naphthyl is substituted with two R^5 groups, wherein one R^5 is cyano and the second R^5 is halogen, alkoxy or cyano. In one embodiment, the naphthyl is substituted with three R^5 groups, wherein one R^5 is cyano and the second R^5 is X-haloalkyl and the third R^5 is -X-L-cycloalkyl.

[0110] In one embodiment wherein R^1 is pyrazolyl, the pyrazolyl is substituted with two R^2 , wherein one R^2 is -X-C1 – C5 alkyl and the second R^2 is -X-aryl optionally substituted with one or more R^5 . In one embodiment, the X is a bond and the aryl is phenyl substituted with three R^5 , wherein (1) each R^5 is independently -X-C1 – C5 alkyl, wherein each X is a bond; (2) one R^5 is cyano and two R^5 are -X-C1 – C5 alkyl, wherein each X is a bond; (3) one R^5 is cyano, one R^5 is halogen, and one R^5 is -X-C1 – C5 alkyl, wherein X is a bond; (4) one R^5 is cyano and two R^5 are alkoxy, (5) one R^5 is cyano and two R^5 are halogens (6) one R^5 is cyano, one R^5 is halogen and one R^5 is alkoxy, (7) or one R^5 is cyano, one R^5 is halogen, and one R^5 is -X-L-cycloalkyl.

[0111] In one embodiment wherein R^1 is pyrazolyl, the pyrazolyl is substituted with two R^2 , wherein one R^2 is -X-C1 – C5 alkyl and the second R^2 is -X-heteroaryl optionally substituted with one or more R^5 . In one embodiment, each X is a bond and the heteroaryl is quinolinyl, pyrazolyl, chromanyl, indoliziny, dihydrobenzylfuranly or imidzaopyridinyl, each optionally substituted with one or more R^5 .

[0112] In one embodiment, the pyrazolyl is substituted with three R^2 , wherein each R^2 is independently -X-C1 – C5 alkyl and each X is a bond.

[0113] In one embodiment wherein R^1 is pyrazolyl, the pyrazolyl is substituted with three R^2 , wherein (1) one R^2 is cyano and two R^2 are halogen; (2) one R^2 is cyano, one R^2 is halogen and one R^2 is alkoxy. In other embodiments, one R^2 is alkoxy, and two R^2 are independently halogen

[0114] In one embodiment for compounds of Formula (I), R^1 is -Y-heteroaryl, Y is a bond and the heteroaryl is imidazolyl, 1*H*-pyrrolopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4*λ*⁴-imidazopyrimidinyl, 2*H*-4*λ*⁴-imidazopyridazinyl, or oxazolopyridyl, each substituted with one R^2 group, wherein R^2 is -X-C1 – C5 alkyl, wherein X is a bond. In one embodiment, the heteroaryl is 1*H*-pyrrolopyridyl substituted with one R^2 , wherein R^2 is cyano or -X-aryl. In certain embodiments, the X of the -X-aryl is a bond and the aryl is phenyl. In one embodiment, the heteroaryl is imidazolyl substituted with one R^2 , wherein R^2 is hydroxyalkyl or -X-aryl.

[0115] In one embodiment for compounds of Formula (I), R^1 is -Y-heteroaryl, Y is a bond and the heteroaryl is imidazopyridyl substituted with one R^2 group, wherein R^2 is cyano, alkoxy, halogen or -X-C1 – C5 alkyl. In other embodiments, the heteroaryl is imidazopyridyl

substituted with two R^2 groups, wherein one R^2 is halogen and the second R^2 group is $-X-C1-C5$ alkyl or halogen.

[0116] In one embodiment for compounds of Formula (I), R^1 is $-Y$ -aryl, Y is $-NR^4-$ and the aryl is phenyl optionally substituted with one or more R^5 .

[0117] In one embodiment, R^1 is $-Y$ - arC1-C3alkyl. In one embodiment, Y is $-NR^4-$ and the arC1-C3alkyl is benzyl.

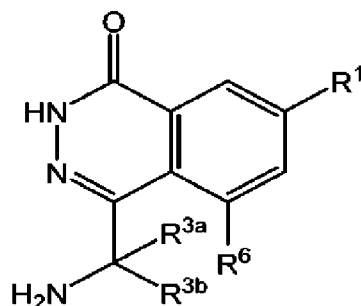
[0118] In one embodiment, R^{3a} and R^{3b} are each hydrogen. In another embodiment, R^{3a} and R^{3b} are each deuterium. In certain embodiments, one of R^{3a} and R^{3b} is hydrogen and the other is deuterium. In one embodiment, R^{3a} and R^{3b} taken together are oxo.

[0119] In one embodiment, each R^4 is hydrogen. In one embodiment, each R^4 is independently C1 – C3 alkyl. In one embodiment, one R^4 is hydrogen and the other R^4 is C1 – C3 alkyl.

[0120] In one embodiment, the cycloalkyl, aryl or heteroaryl rings are optionally substituted with one or more R^5 , wherein R^5 is cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, $-X$ -haloalkyl, $-Z$ -cycloalkyl, $-X$ -arC1-C3alkyl, $-X$ -L-cycloalkyl or $-X$ -aryl.

[0121] In one embodiment, R^6 is hydrogen. In one embodiment, R^6 is halogen. In certain embodiments, the halogen is chlorine or fluorine. In one embodiment, R^6 is C1 – C3 alkyl. In certain embodiments, the C1 – C3 alkyl is methyl or ethyl. In one embodiment, R^6 is alkoxy. In certain embodiments, the alkoxy is methoxy. In one embodiment, R^6 is haloalkyl. In certain embodiments, the haloalkyl is trifluoromethyl.

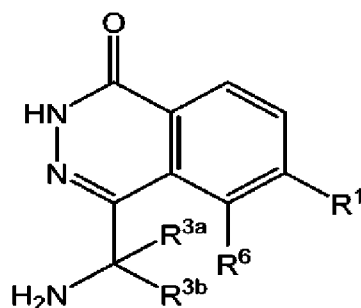
[0122] In one aspect of the invention, compounds are provided that are represented by Formula (I-A):



Formula (I-A)

[0123] or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z, and L are as each defined for Formula I.

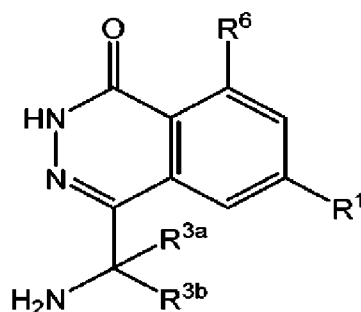
[0124] In one aspect of the invention, compounds are provided that are represented by Formula (I-B):



Formula (I-B)

[0125] or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z, and L are as each defined for Formula I.

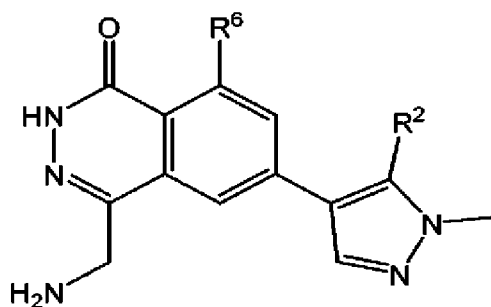
[0126] In one aspect of the invention, compounds are provided that are represented by Formula (I-C):



Formula (I-C)

[0127] or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , Y, X, Z and L are as each defined for Formula I.

[0128] In another aspect of the invention, compounds are provided that are represented by Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

each Y is independently a bond or -NR⁴-;

each R² is independently hydroxy, halogen, cyano, cyanomethyl, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵, or;

each X is independently a bond, O, S, -NR⁴- or -NR⁴C(O)-;

each Z is independently a bond, -SO-, -SO₂-, -CH(OH)- or -C(O)-;

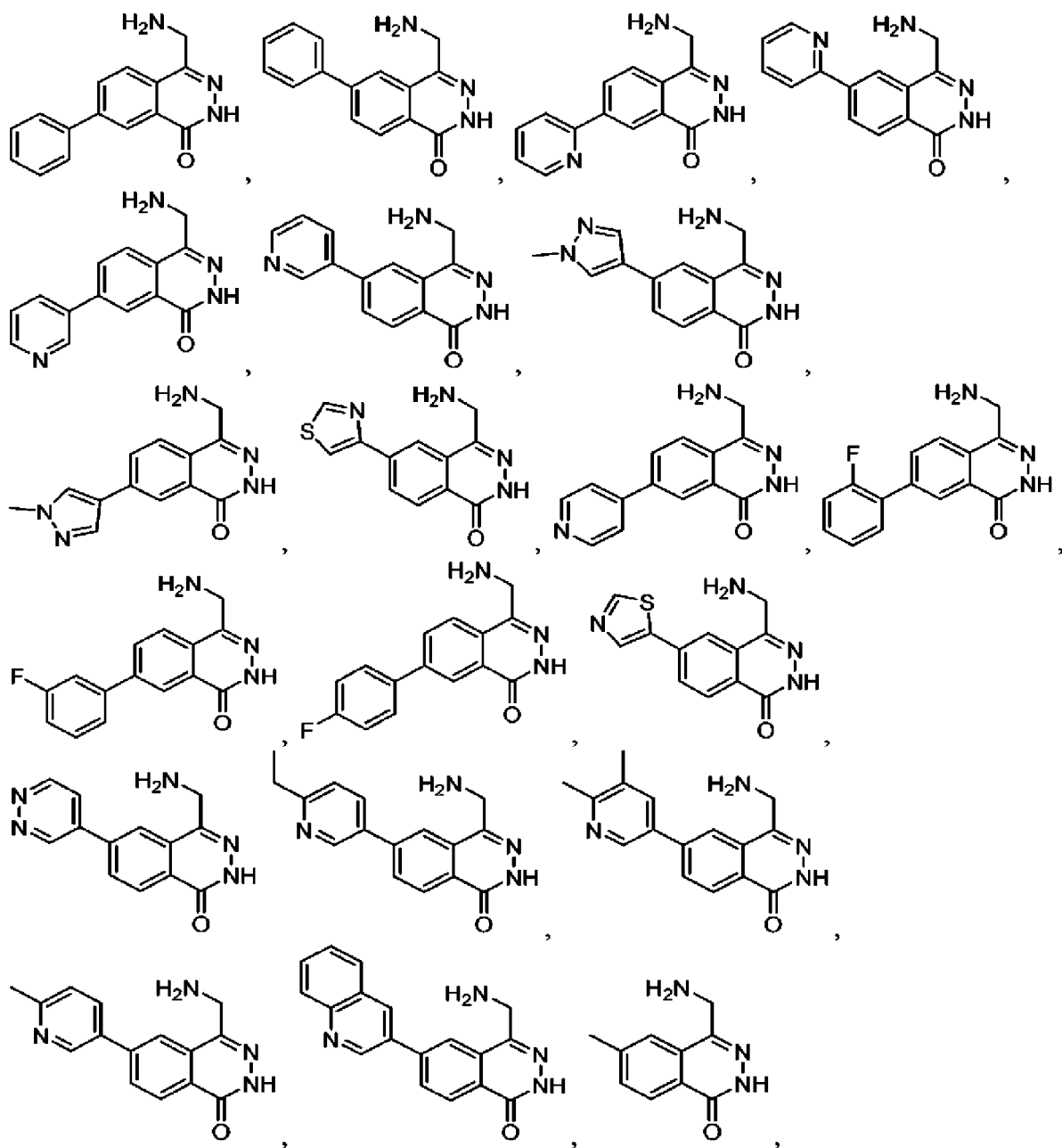
each L is independently a bond or C1 – C3 alkylene;

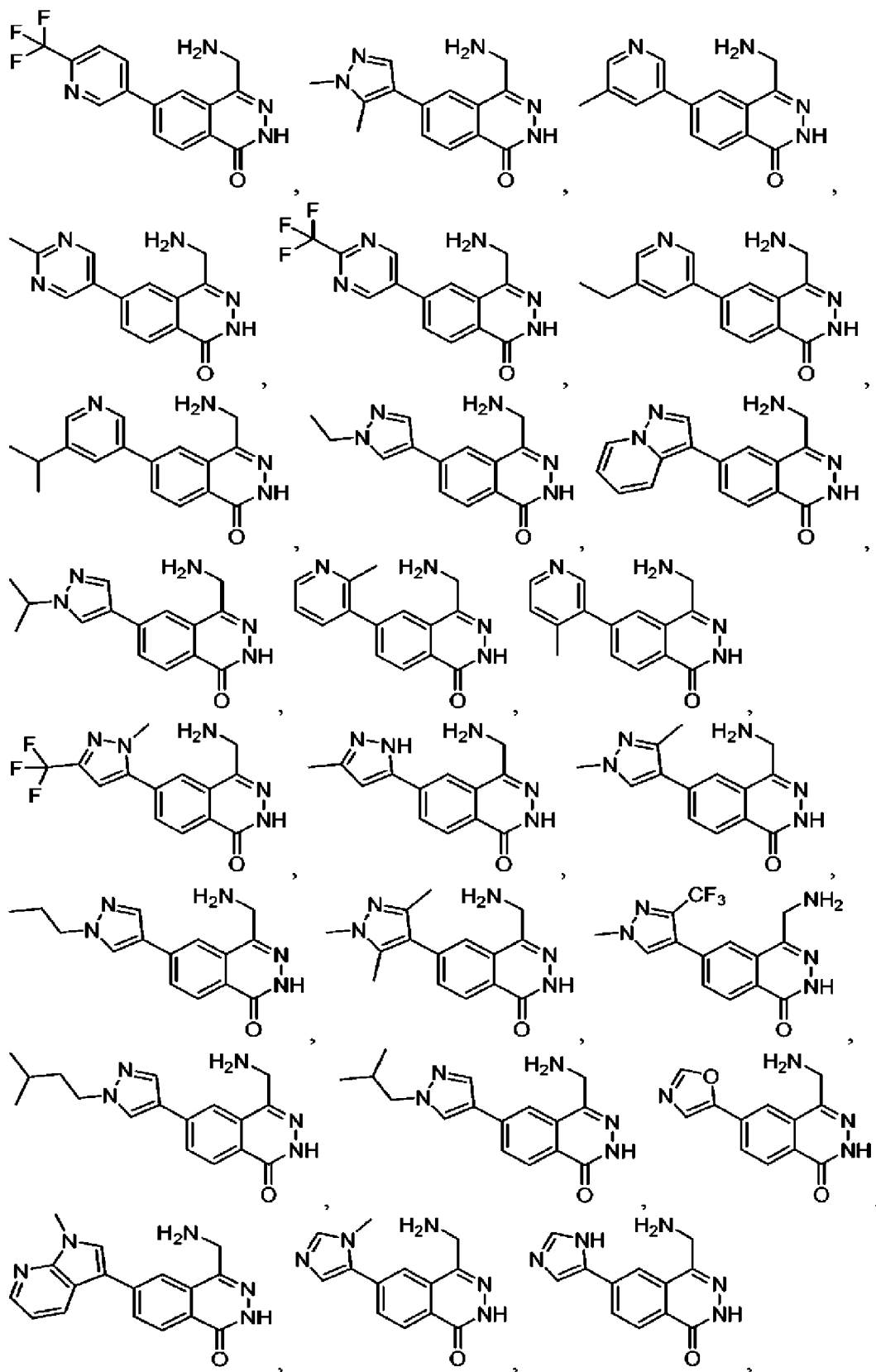
each R⁴ is independently hydrogen or C1 – C3 alkyl;

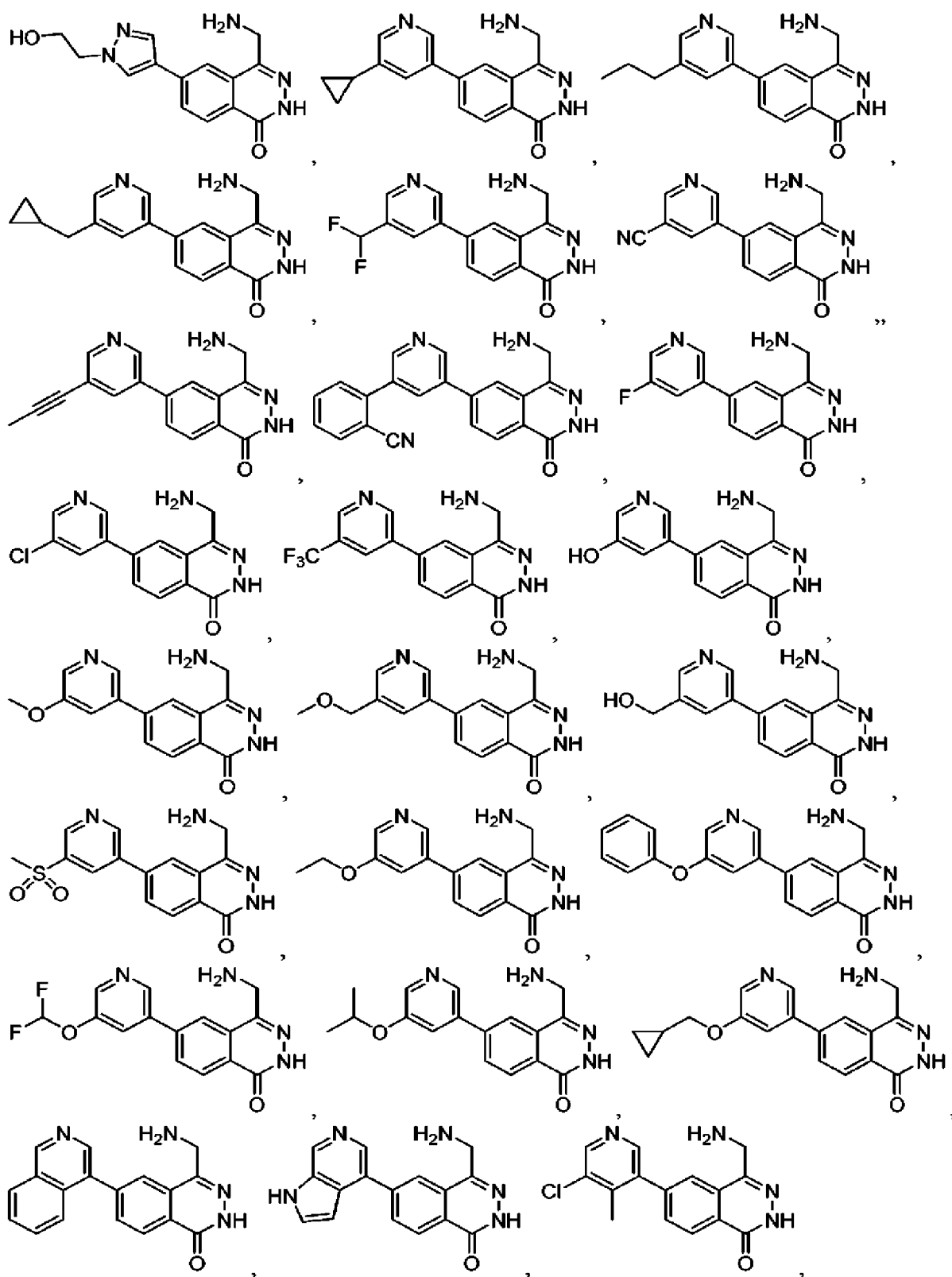
each R⁵ is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

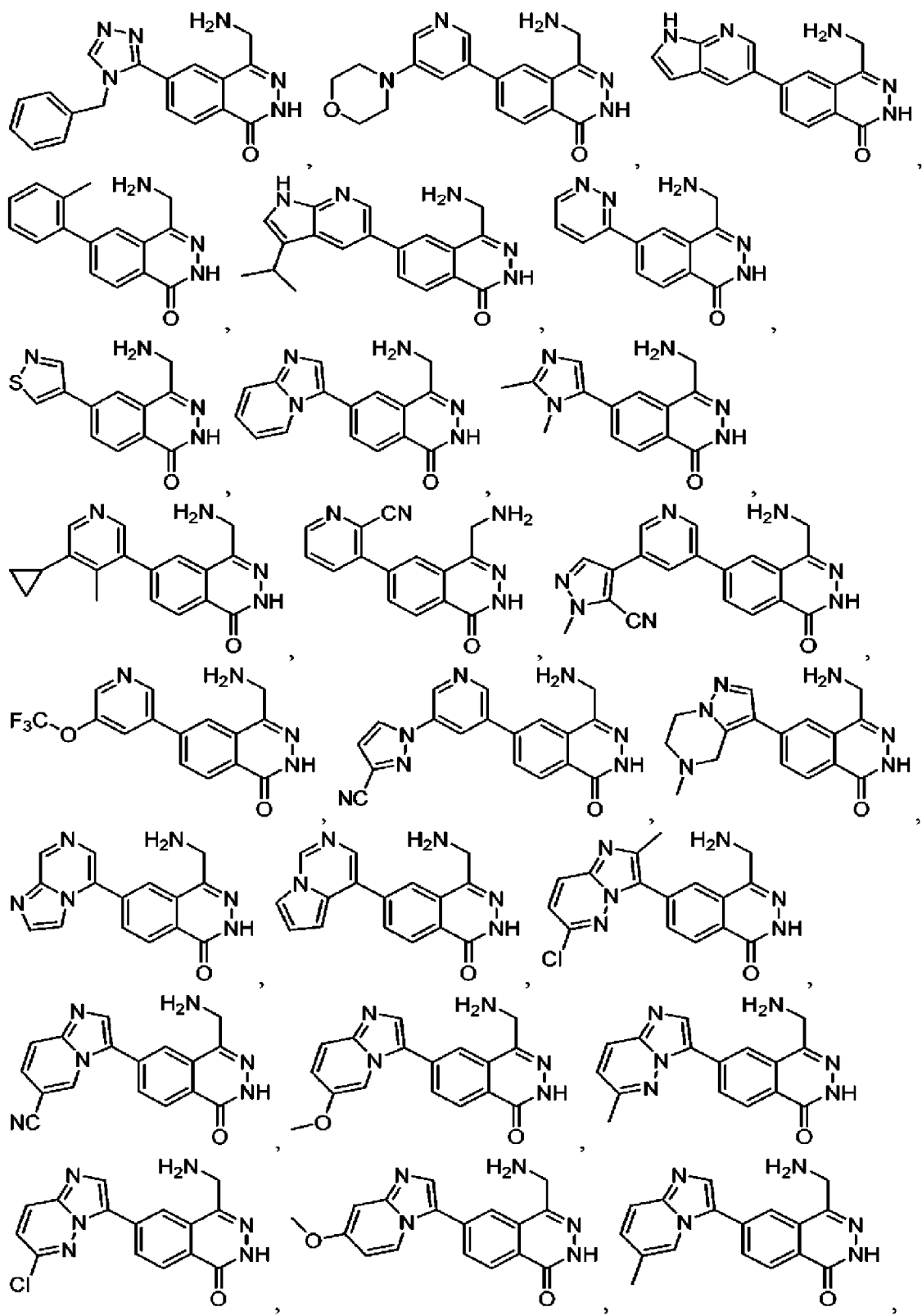
R⁶ is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

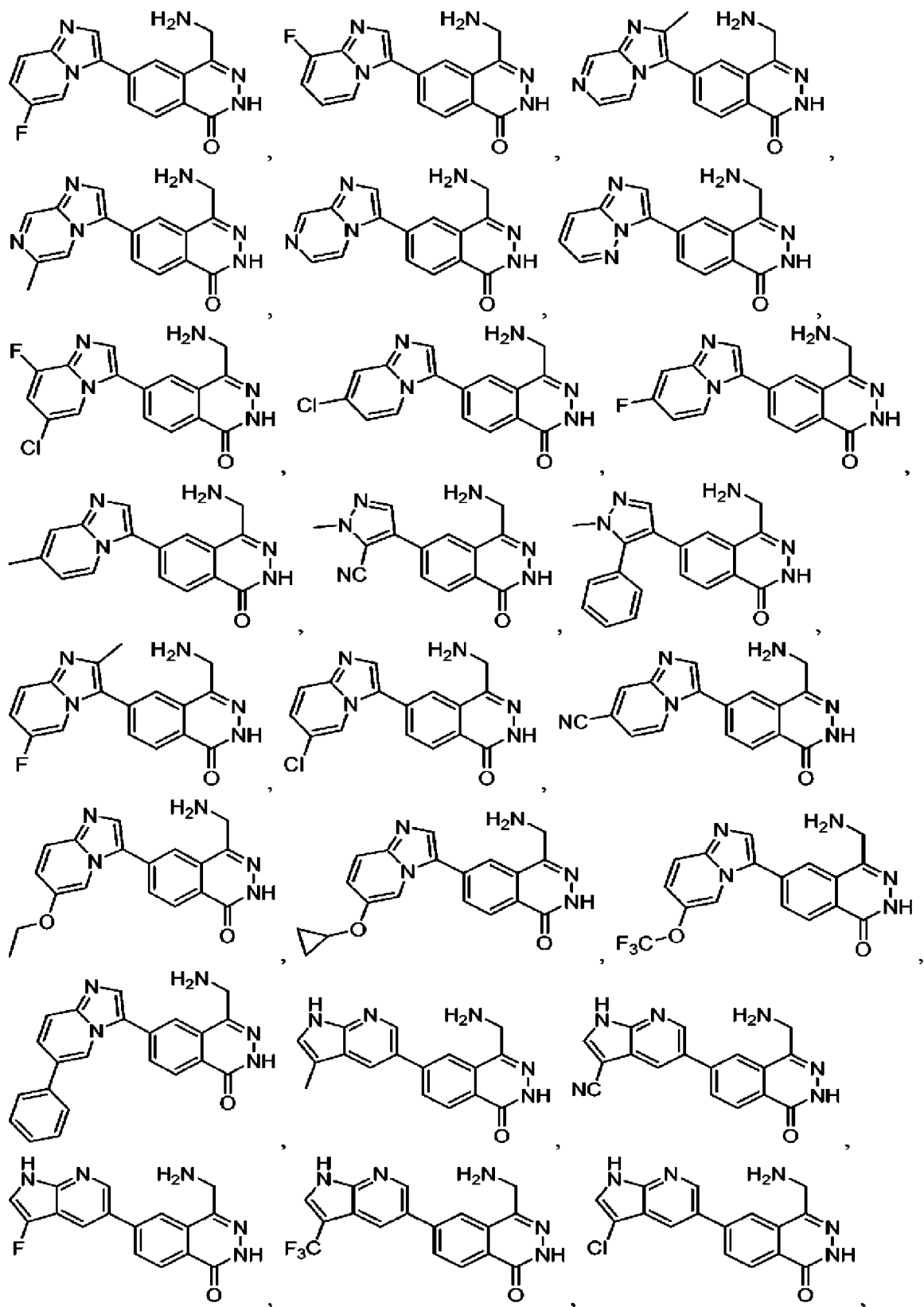
[0129] In one embodiment, the compound of Formula (I), Formula (I-A), Formula (I-B), and/or Formula (I-C) is:

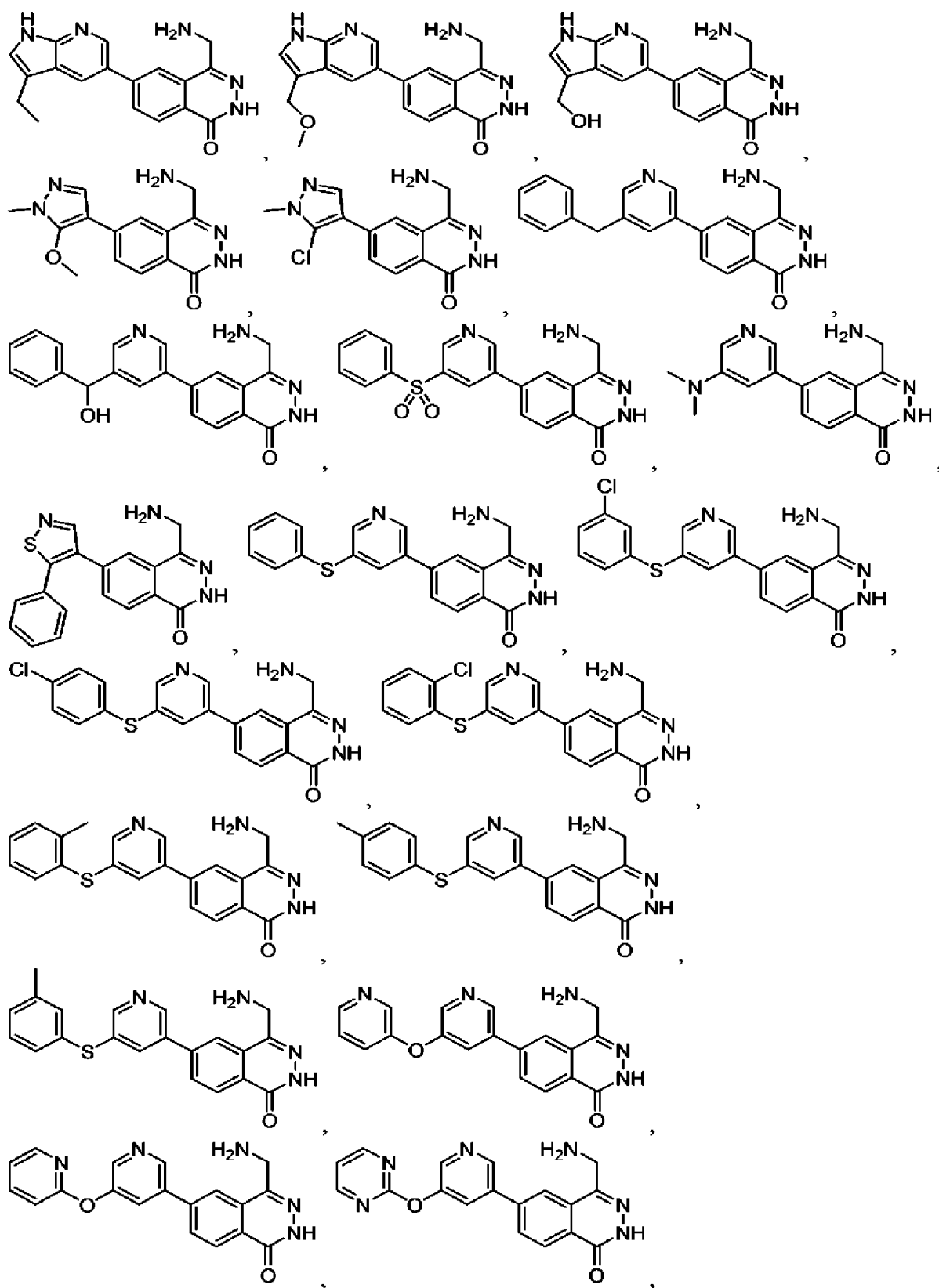


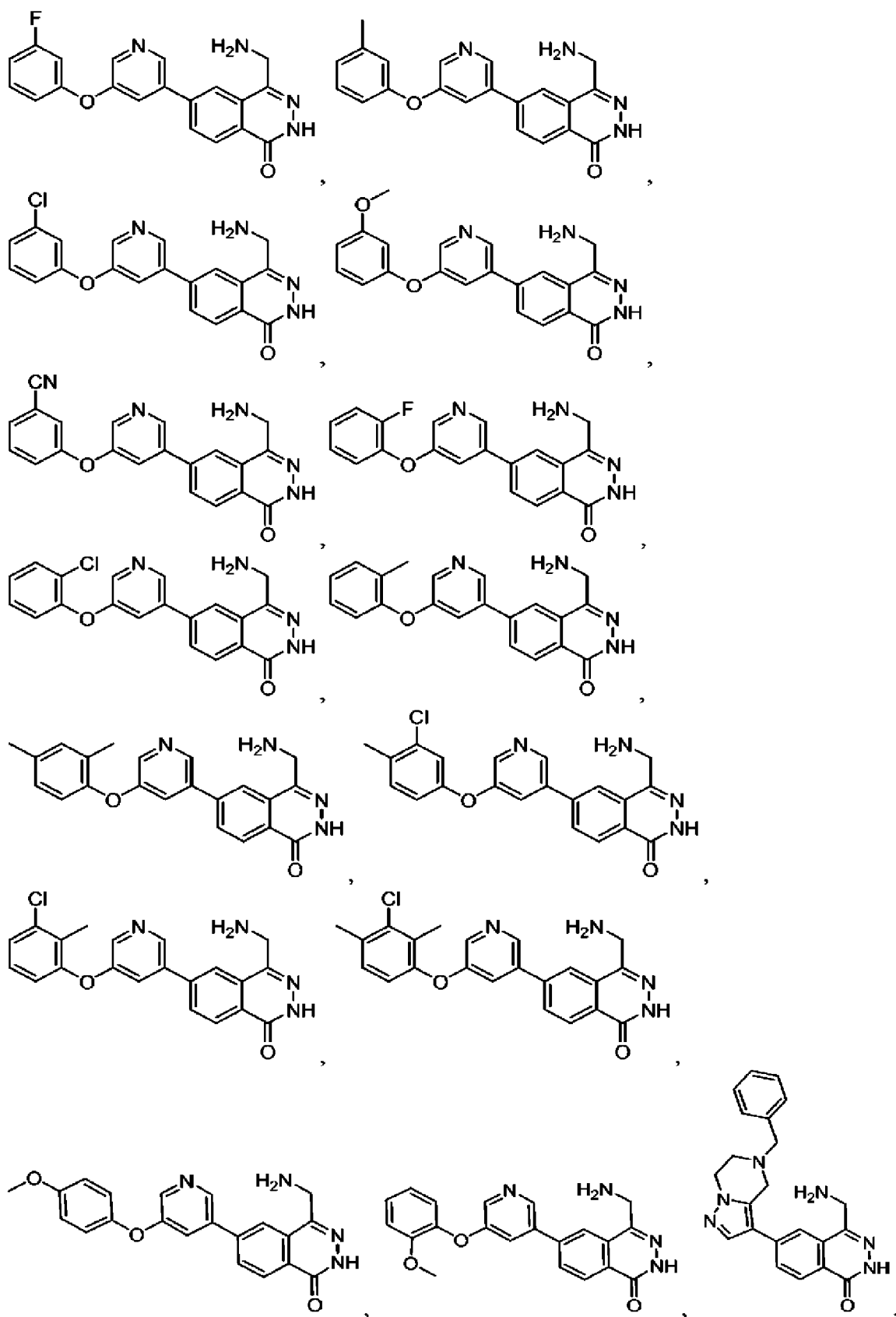




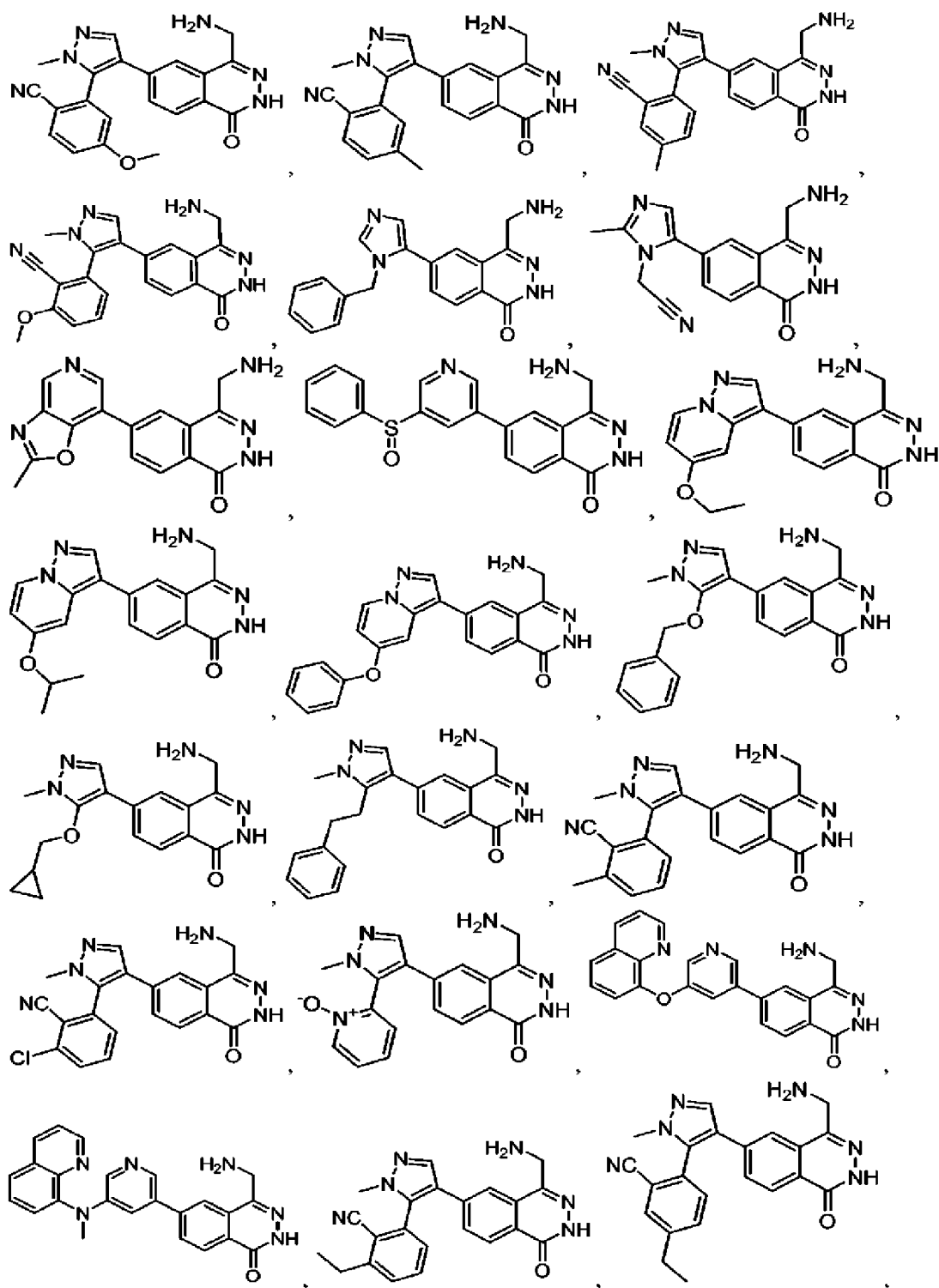


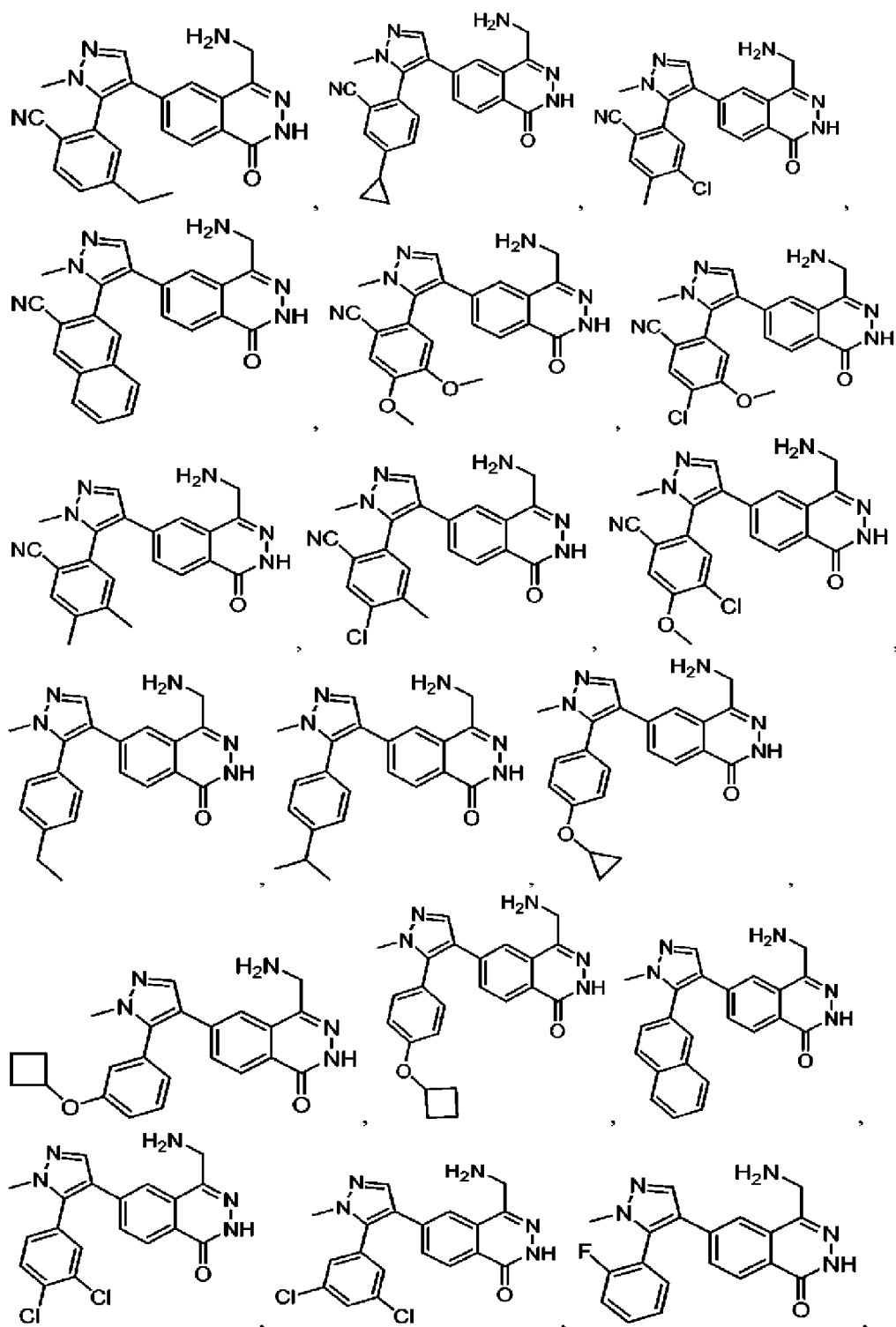


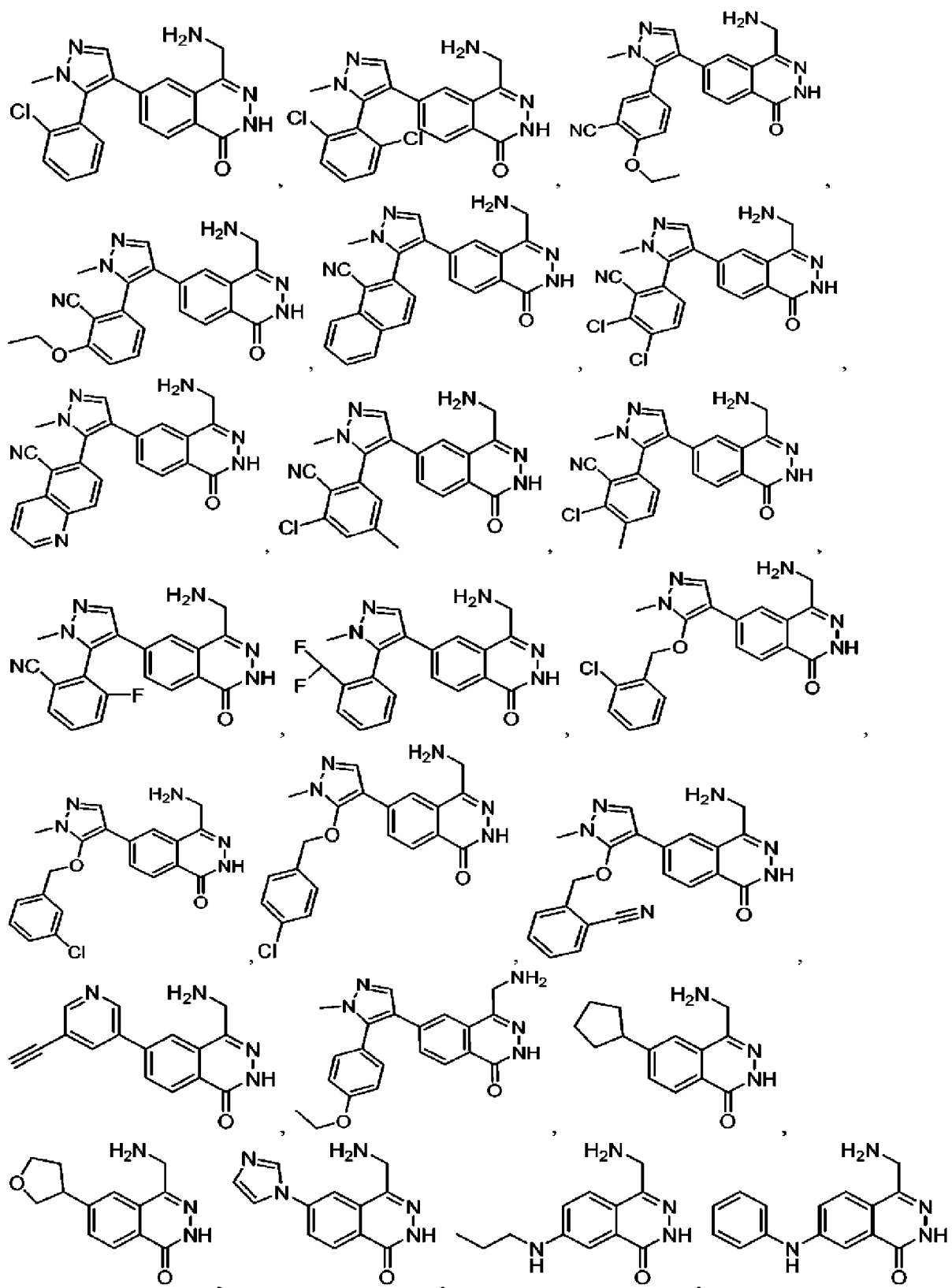


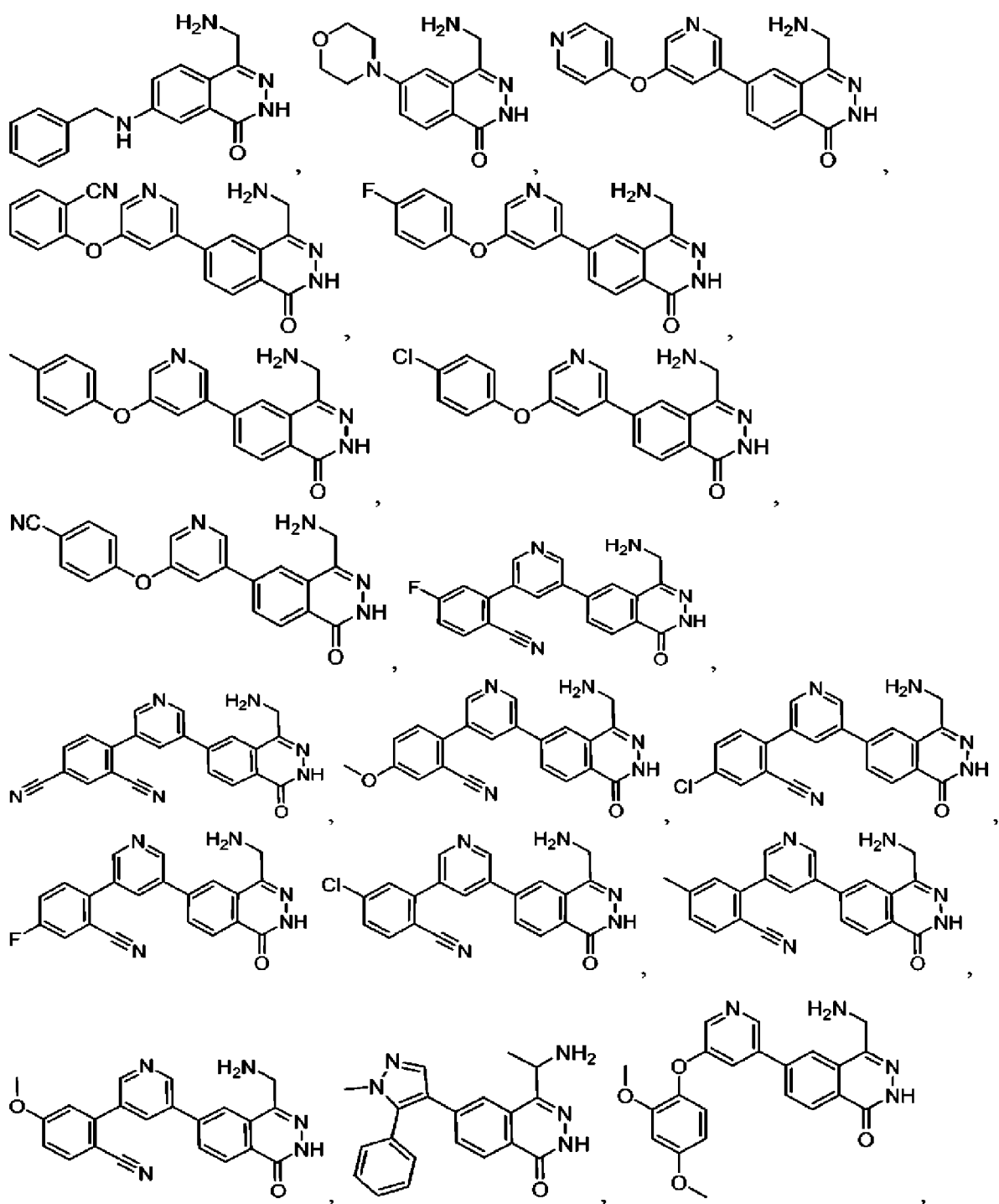


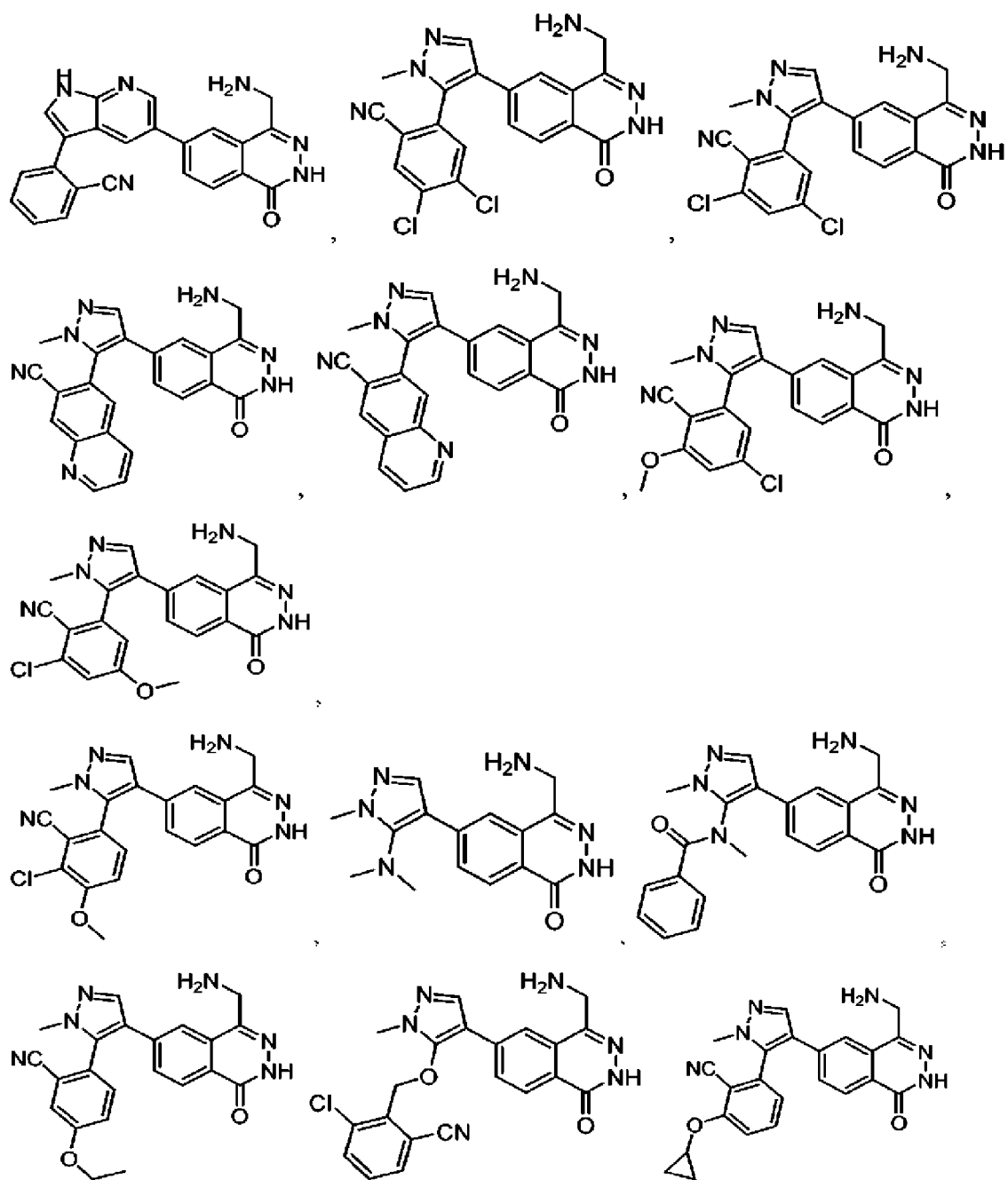


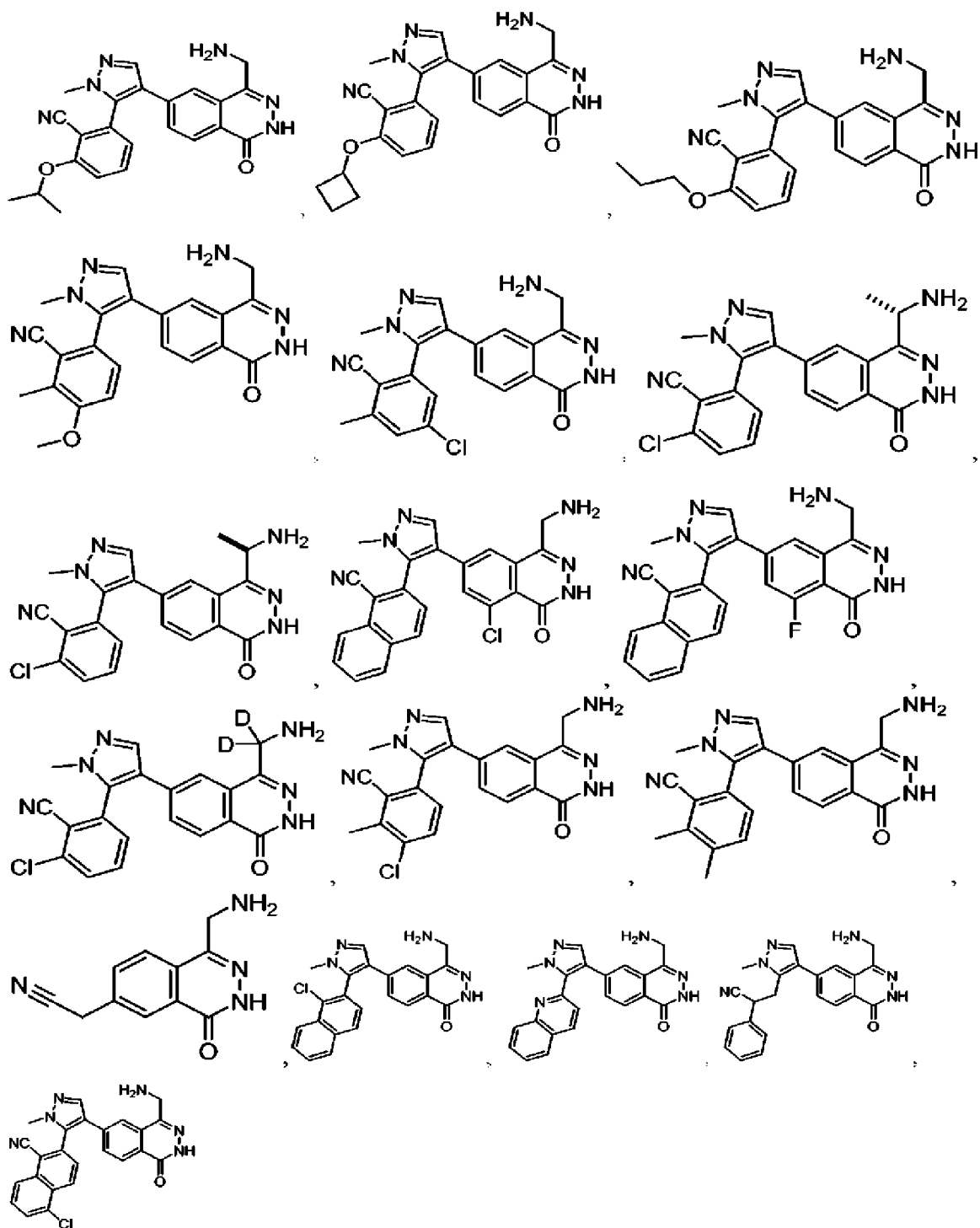


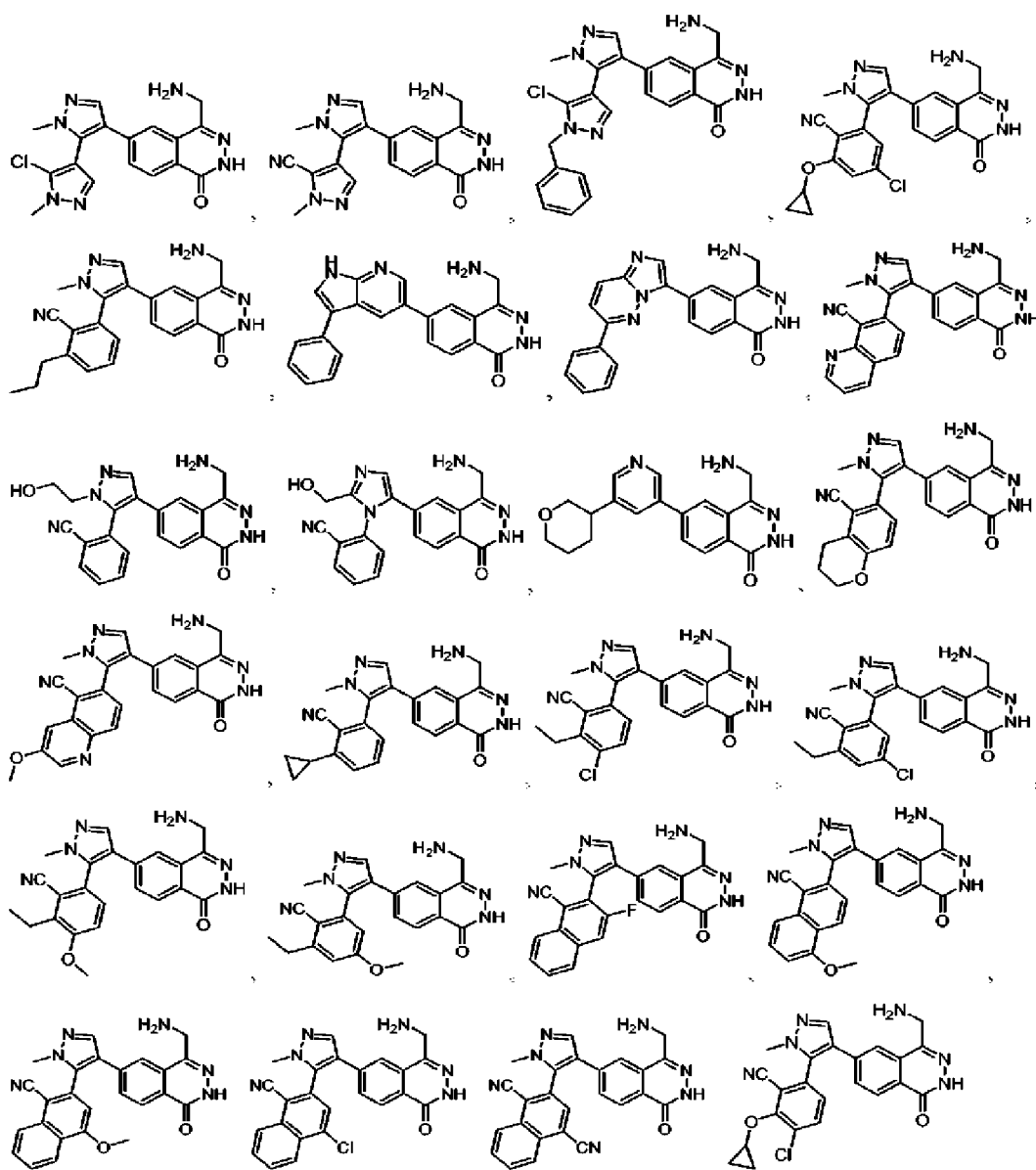


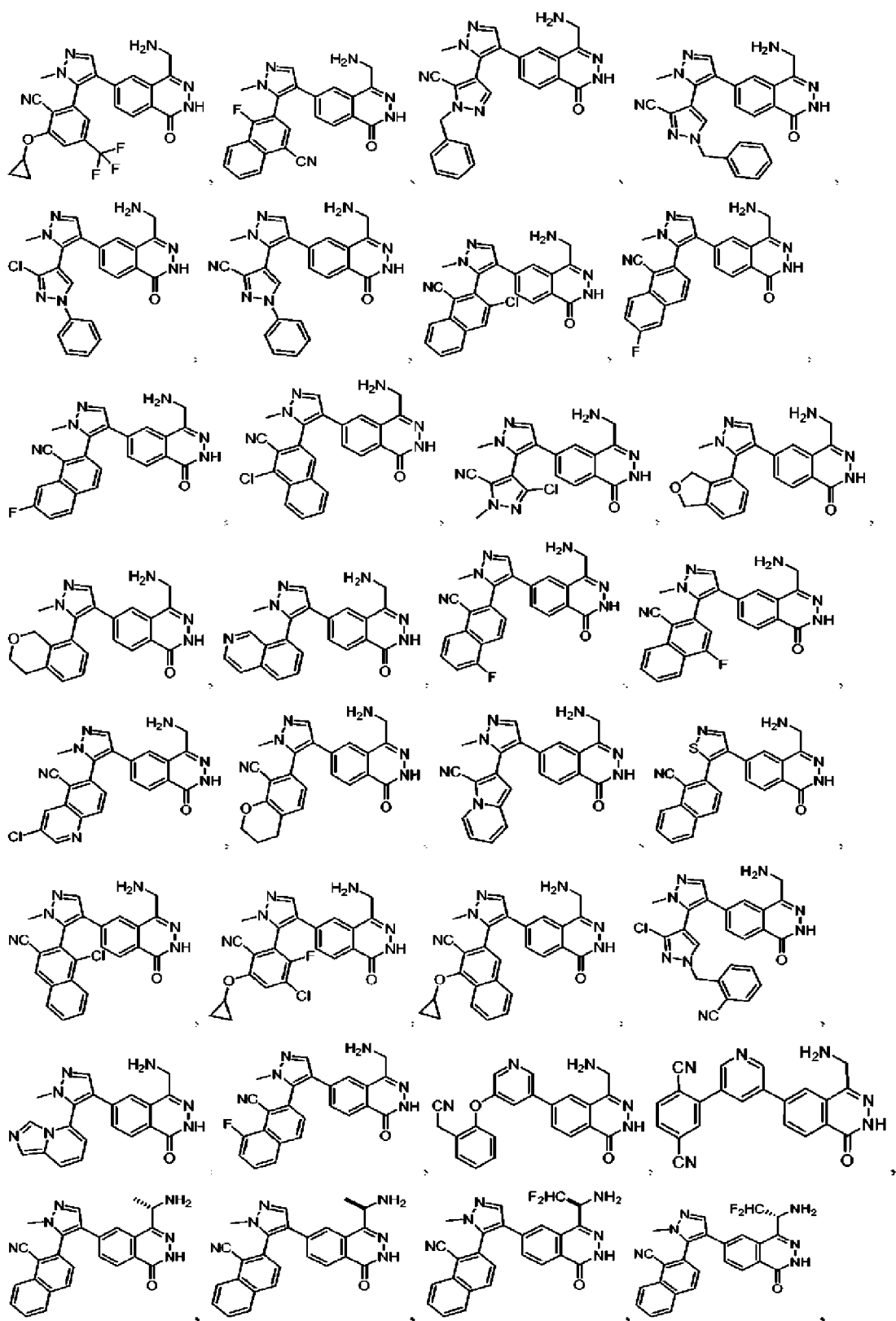


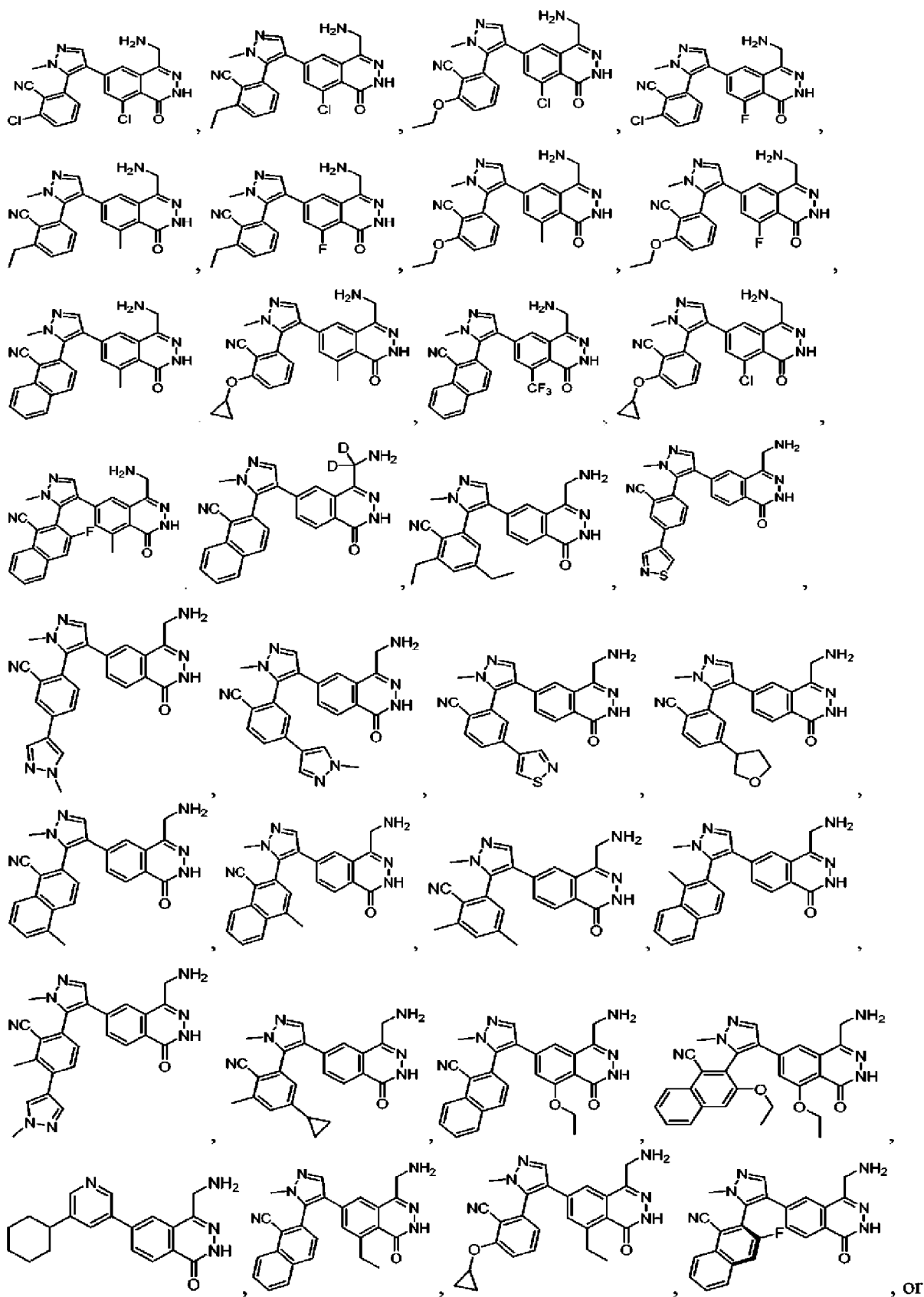




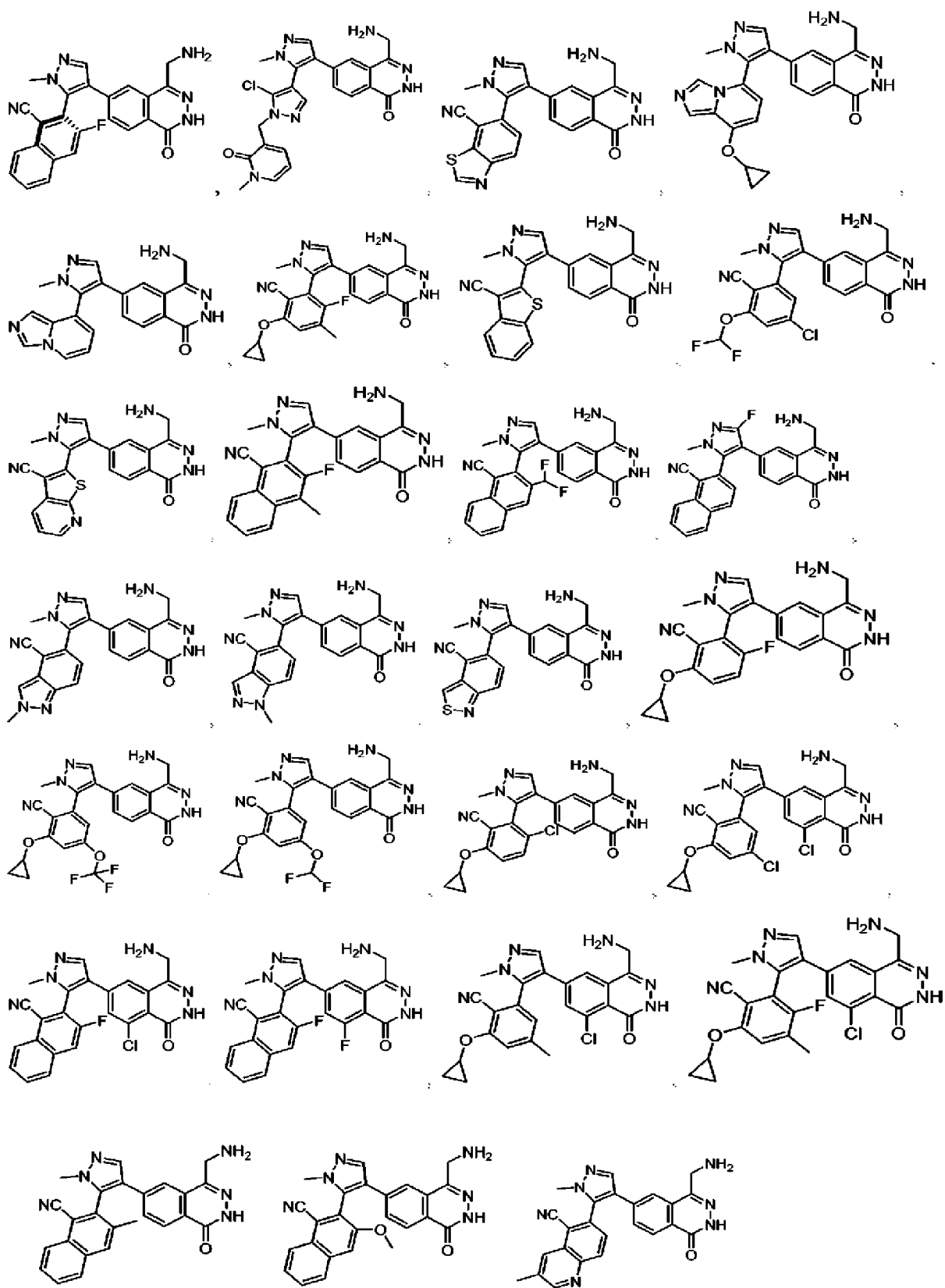


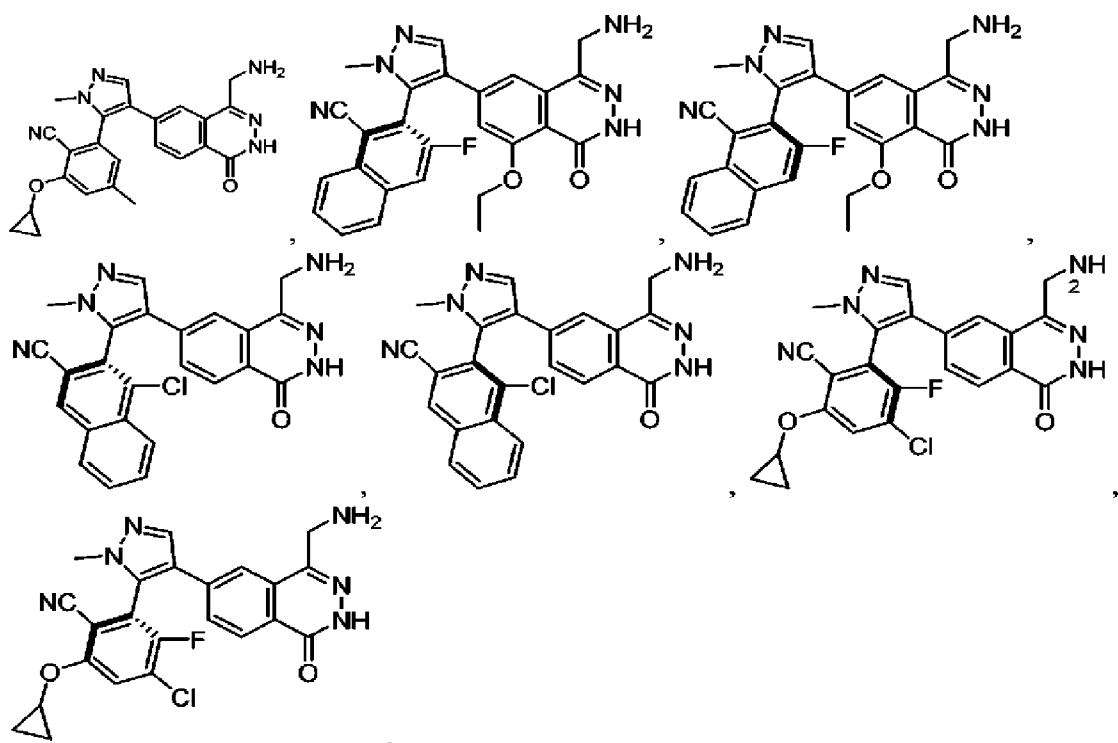






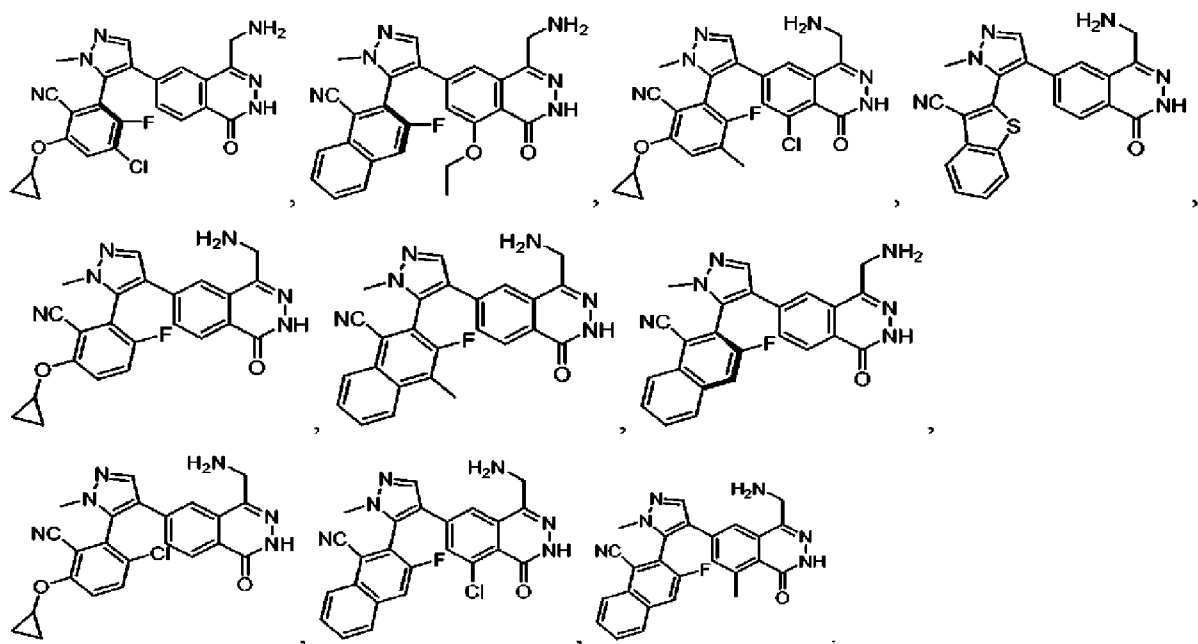
, or





and pharmaceutically acceptable salts of the foregoing compounds.

[0130] In one embodiment, the compound of Formula (I) is:



or a pharmaceutically acceptable salt of the foregoing compounds.

[0131] The compounds of Formula (I), Formula (I-A), Formula (I-B) and Formula (I-C) may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0132] In another aspect, the invention provides pharmaceutical compositions comprising a PRMT5 inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be by the oral route.

[0133] The characteristics of the carrier will depend on the route of administration. As used herein, the term “pharmaceutically acceptable” means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington’s Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0134] As used herein, the term “pharmaceutically acceptable salts” refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+Z^-$,

wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, --O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0135] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0136] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods described herein.

METHODS OF USE

[0137] In yet another aspect, the invention provides for methods for inhibiting PRMT5 activity in a cell, comprising contacting the cell in which inhibition of PRMT5 activity is desired in vitro with an effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B) or Formula (I-C), pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof. In one embodiment, the cell is an MTAP-deficient cell.

[0138] The compositions and methods provided herein are particularly deemed useful for inhibiting PRMT5 activity in a cell in vivo. In one embodiment, a cell in which inhibition of PRMT5 activity is desired is contacted in vivo with a therapeutically effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, to negatively modulate the activity of PRMT5. In other embodiments, a therapeutically effective amount of pharmaceutically acceptable salt or pharmaceutical compositions containing the compound of Formula (I), Formula (I-A), Formula (I-B) or Formula (I-C) may be used. In one embodiment, the cell is an MTAP-

deficient cell. In one embodiment, the negatively modulating the activity of PRMT5 occurs in the presence of bound MTA.

[0139] By negatively modulating the activity of PRMT5, particularly in cases for cells that lack MTAP activity, the methods are designed to inhibit PRMT5 activity to block cellular proliferation. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to affect the desired negative modulation of PRMT5. The degree PRMT5 inhibition may be monitored in vitro against the enzyme in the presence and absence of MTA and in the cell using well known methods, including those described in Example B below, to assess the effectiveness of treatment and dosages.

[0140] In another aspect, methods of treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B) of Formula (I-C), pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided. In one embodiment, the cancer is an MTAP-associated cancer.

[0141] The compositions and methods provided herein may be used for the treatment of a wide variety of cancer including tumors such as prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell

carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL).

[0142] In one embodiment, the cancer is an MTAP-associated cancer selected from hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, and head and neck cancer.

[0143] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-

administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

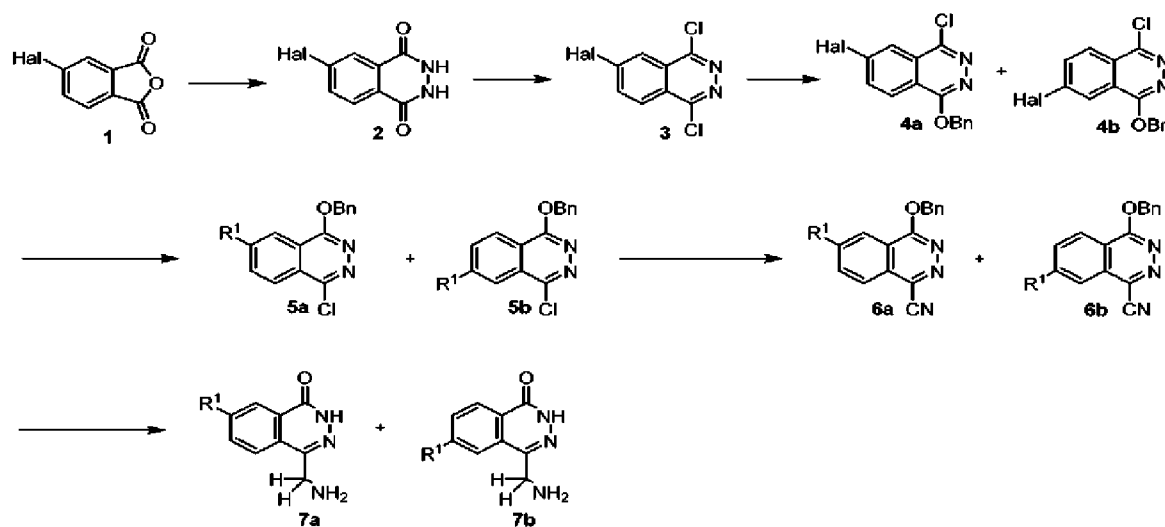
GENERAL REACTION SCHEMES, INTERMEDIATES AND EXAMPLES

GENERAL REACTION SCHEMES

[0144] The compounds of the present invention may be prepared using commercially available reagents and intermediates in the synthetic methods and reaction schemes described herein, or may be prepared using other reagents and conventional methods well known to those skilled in the art.

[0145] For instance, intermediates for preparing compounds and compounds of Formula (I), Formula (I-A), Formula (I-B) or Formula (I-C) of the present invention may be prepared according to General Reaction Schemes I - XVI:

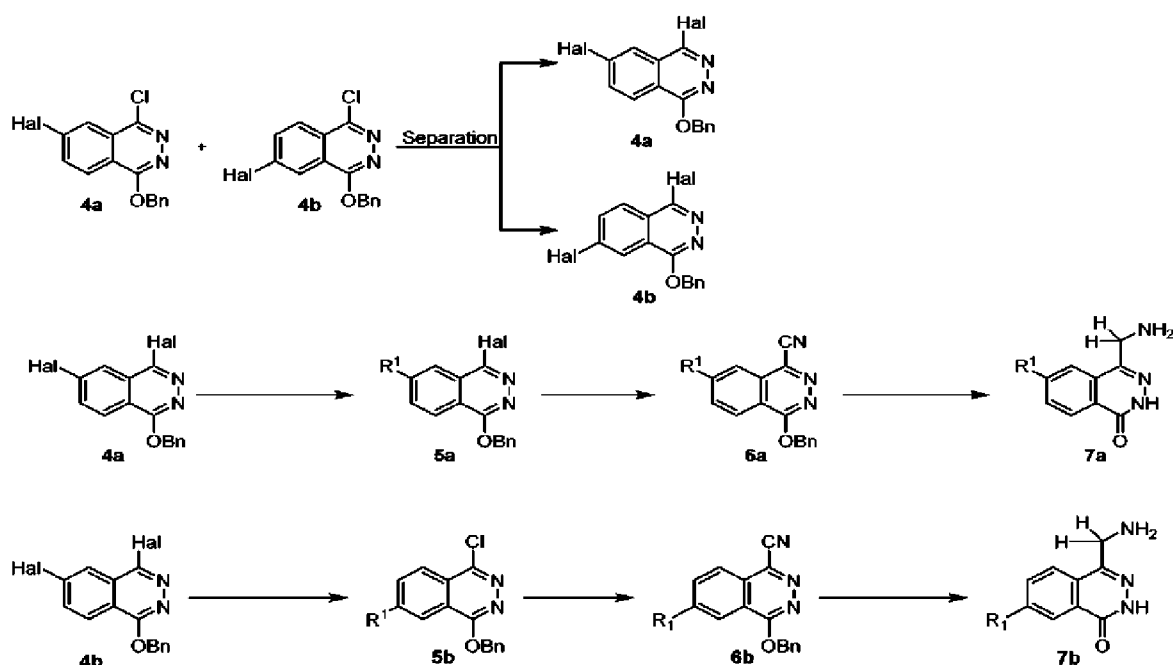
GENERAL REACTION SCHEME I



[0146] Compounds of Formula (I) wherein R¹ is aryl or heteroaryl, may be prepared according to General Reaction Scheme I. Compounds 7a and 7b are both examples of Formula (I) wherein R¹ is aryl or heteroaryl and R^{3a} and R^{3b} are H. A haloaryl cyclic anhydride 1 is treated with bis(nucleophile) such as hydrazine hydrate in acetic acid at elevated temperature, to form a phthalhydrazide 2 which is treated with a halogenating agent, for example POCl₃ to afford the trihalophthalazine 3. Treatment of the trihalophthalazine 3 with

an alcohol, for example benzyl alcohol and NaH in THF at 0°C, furnishes dihaloalkoxyphthalazine **4a** and **4b** as a mixture of regioisomers. The mixture of **4a** and **4b** is subjected to palladium catalyzed cross coupling conditions, such as the Stille coupling or the Suzuki coupling with aryl/heteroaryl metal reactants, for example with the corresponding aryl/heteroaryl-tributyltin or aryl/heteroaryl boronic acids/esters to provide substituted haloalkoxyphthalazine **5a** and **5b** as a mixture of regioisomers. The substituted haloalkoxyphthalazine mixture **5a** and **5b** is subjected to metal-mediated cyanation conditions with for example, Pd₂(dba)₃, dppf, Zn and ZnCN₂ in DMF at elevated temperature and the resulting cyanoalkoxyphthalazine mixture **6a** and **6b** is subjected to hydrogenation conditions, for example with Pd/C, HCl and H₂ in methanol to give the phthalazinone methylamine mixture **7a** and **7b**. The regioisomeric mixture of **7a** and **7b** is separated by chromatography, such as supercritical fluid chromatography (SFC) to furnish the desired compounds **7a** and **7b** of Formula (I).

GENERAL REACTION SCHEME II

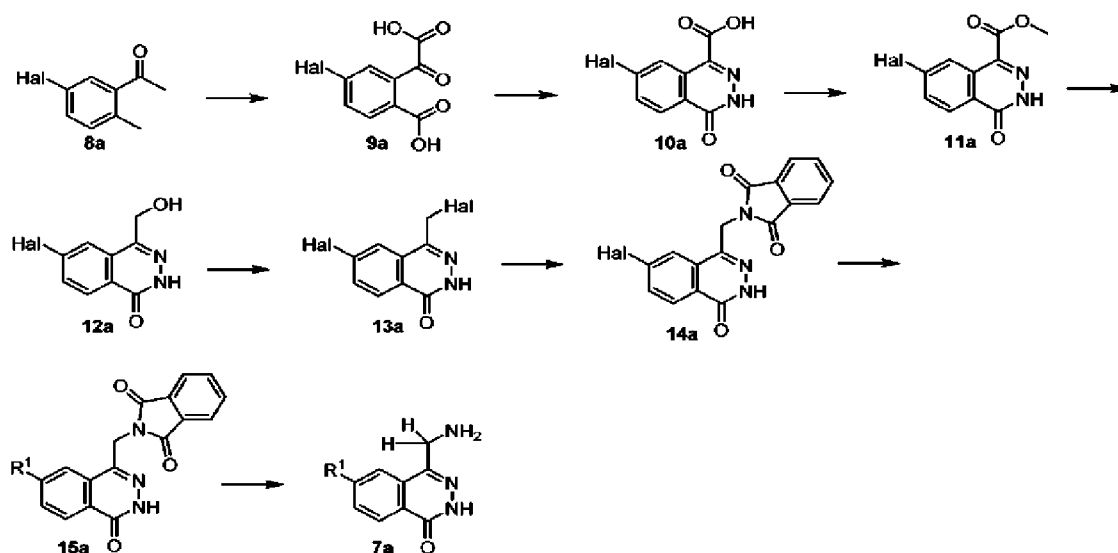


Wherein R¹ = Aryl/Heteroaryl, Hal = Cl, Br, or I

[0147] Compounds of Formula (I) wherein R¹ is aryl or heteroaryl, may be prepared according to General Reaction Scheme II. Compounds **7a** and **7b** are both examples of Formula (I) wherein R¹ is aryl or heteroaryl and R^{3a} and R^{3b} are H. The mixture of

regioisomers **4a** and **4b** are separated by chromatography, such as supercritical fluid chromatography (SFC) giving isomerically pure dihaloalkoxyphthalazines **4a** and **4b**. **4a** or **4b** is then subjected to metal-mediated cross coupling conditions, for example Suzuki conditions, with aryl/heteroaryl boronic acids/esters to provide the substituted haloalkoxyphthalazine **5a** or **5b**. The substituted haloalkoxyphthalazine **5a** or **5b** is subjected to metal-mediated cyanation conditions with for example, $\text{Pd}_2(\text{dba})_3$, dppf, Zn and ZnCN_2 in DMF at elevated temperature to furnish cyanoalkoxyphthalazine **6a** or **6b**. Cyanoalkoxyphthalazine **6a** or **6b** is subjected to hydrogenation conditions, for example with Pd/C, HCl and H_2 in methanol to give the phthalazinone **7a** or **7b** to furnish the desired compounds of Formula (I).

GENERAL REACTION SCHEME III-A

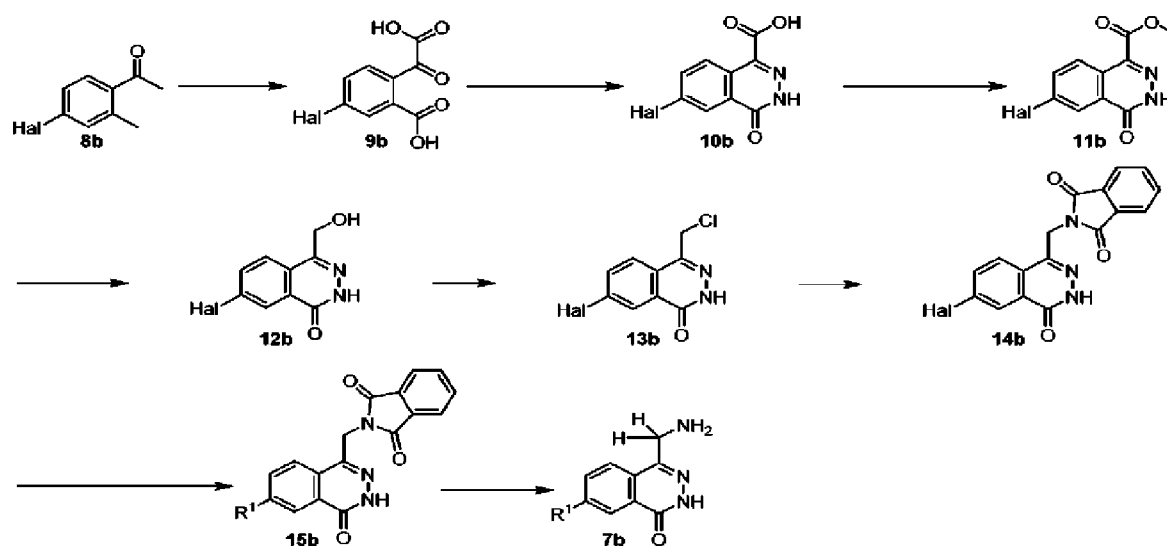


Wherein R^1 = Aryl, heteroaryl, alkyl and Hal = Cl, Br, or I

[0148] Compounds of Formula (I) wherein R^1 is aryl, heteroaryl, heterocyclyl or alkyl, may be prepared according to General Reaction Scheme III-A. Compound **7a** is an example of Formula (I) wherein R^1 is aryl, heteroaryl, heterocyclyl or alkyl and R^{3a} and R^{3b} are H. 1-(5-halo-2-methylphenyl)ethenone **8a** is treated with an oxidant, for example KMnO_4 in water at 50°C to furnish 2-(carboxycarbonyl)-4-halobenzoic acid **9a**. Condensation of **9a**, for example with hydrazine hydrate in ethanol at elevated temperature, yields 7-halo-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid **10a** which is then esterified with acid and alcohol, for example sulfuric acid and methanol. Methyl 7-halo-4-oxo-3,4-dihydrophthalazine-1-carboxylate **11a** is reduced via hydride reduction, for example with sodium borohydride and

CaCl₂ in methanol, to afford the 6-halo-4-(hydroxymethyl)phthalazin-1(2H)-one **12a**, which is then treated with halogenating agent, for example thionyl chloride for 12 hours to provide 6-halo-4-(halomethyl)phthalazin-1(2H)-one **13a**. Nucleophilic S_N2 displacement of **13a** with a nitrogen nucleophile for example, potassium phthalimide in DMF at elevated temperature furnishes **14a** which is subjected to metal-mediated cross coupling conditions, for example Suzuki conditions, with aryl/heteroaryl/heterocyclyl/alkyl boronic acids/esters to provide phthalazinone coupling product **15a**. The phthalimide protecting group of **15a** is removed under solvolysis conditions, for example with hydrazine hydrate in ethanol to furnish the desired compound **7a** of Formula (I).

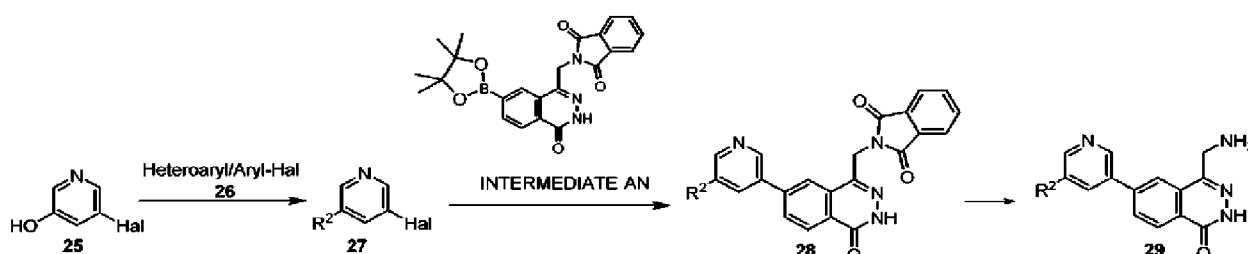
GENERAL REACTION SCHEME III-B



[0149] Compounds of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl, may be prepared according to General Reaction Scheme III-B. Compound **7b** is an example of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl and R^{3a} and R^{3b} are H. 1-(5-halo-2-methylphenyl)ethenone **8b** is treated with an oxidant, for example KMnO₄ in water at 50°C to furnish 2-(carboxycarbonyl)-4-halobenzoic acid **9b**. Condensation of **9b**, for example with hydrazine hydrate in ethanol at elevated temperature, yields 7-halo-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid **10b** which is then esterified with acid and alcohol, for example sulfuric acid and methanol. Methyl 7-halo-4-oxo-3,4-dihydrophthalazine-1-carboxylate **11b** is reduced via hydride reduction, for example with sodium borohydride and CaCl₂ in methanol, to afford the 6-halo-4-(hydroxymethyl)phthalazin-1(2H)-one **12b**, which

is then treated with halogenating agent, for example thionyl chloride for 12 hours to provide 6-halo-4-(halomethyl)phthalazin-1(2H)-one **13b**. Nucleophilic S_N2 displacement of **13b** with a nitrogen nucleophile for example, potassium phthalimide in DMF at elevated temperature furnishes **14b** which is subjected to metal-mediated cross coupling conditions, for example Suzuki conditions, with aryl/heteroaryl/heterocyclyl/alkyl boronic acids/esters to provide phthalazinone coupling product **15b**. The phthalimide protecting group of **15b** is removed under solvolysis conditions, for example with hydrazine hydrate in ethanol to furnish the desired compound **7b** of Formula (I).

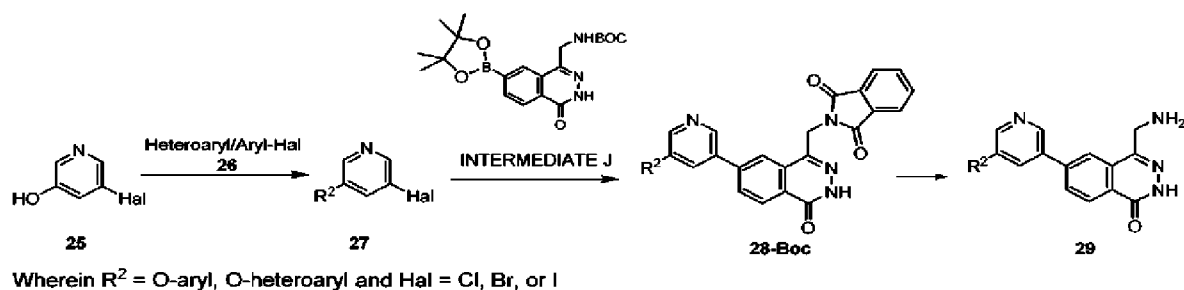
GENERAL REACTION SCHEME IV-A



Wherein R² = O-aryl, O-heteroaryl and Hal = Cl, Br, or I

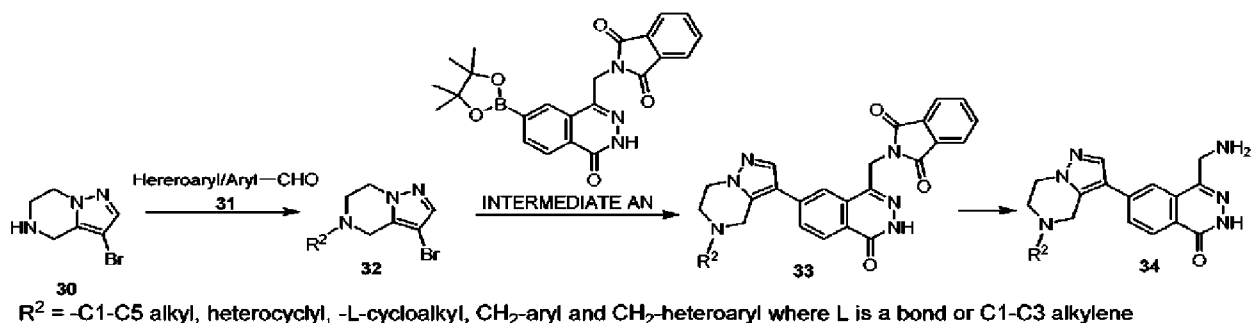
[0150] Compounds of Formula (I) wherein R¹ is pyridyl and R² is -O-aryl or -O-heteroaryl, may be prepared according to General Reaction Scheme IV-A. Compound **29** is an example of Formula (I) wherein R¹ is pyridyl, R² is -O-aryl or -O-heteroaryl, and R^{3a} and R^{3b} are H. 5-bromopyridin-3-ol **25** is heated with an appropriately substituted aryl/heteroaryl halide **26**, for example in a mixture of DMF and NaH, to furnish 3-halo-5-R²-oxypyridine **27**. 3-halo-5-R²-pyridine **27** is coupled to boronic acid, Intermediate AN under palladium catalyzed cross coupling conditions, for example the Suzuki coupling, to generate R²-pyridyl coupling product **28**. R²-pyridyl coupling product **28** is subjected to solvolysis conditions, for example with hydrazine hydrate in ethanol, to furnish the free amine **29** of Formula (I).

GENERAL REACTION SCHEME IV-B



[0151] Compounds of Formula (I) wherein *R*¹ is pyridyl and *R*² is -O-aryl or -O-heteroaryl, may be prepared according to General Reaction Scheme IV-B. Compound **29** is an example of Formula (I) wherein *R*¹ is pyridyl, *R*² is -O-aryl or -O-heteroaryl, and *R*^{3a} and *R*^{3b} are H. 5-bromopyridin-3-ol **25** is heated with aryl/heteroaryl halide **26**, for example in a mixture of DMF and NaH, to furnish 3-bromo-5-*R*²-pyridine **27**. 3-bromo-5-*R*²-pyridine **27** is coupled to boronic acid Intermediate J under palladium catalyzed cross coupling conditions, for example Suzuki conditions, to generate coupling product **28-Boc**. Coupling product **28-Boc** is subjected to acidic conditions, for example with TFA, to furnish the desired compound **29** of Formula (I).

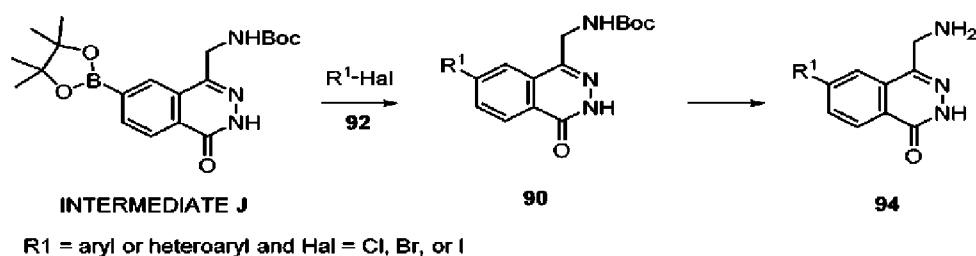
GENERAL REACTION SCHEME IV-C



[0152] Compounds of Formula (I) wherein *R*¹ is 5-*R*²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl and *R*² is -C1 - C5 alkyl, heterocyclyl, -L-cycloalkyl, -CH₂-aryl and -CH₂-heteroaryl where L is a bond or C1 - C3 alkylene, may be prepared according to General Reaction Scheme IV-C. Compound **34** is an example of Formula (I) wherein *R*¹ is 5-*R*²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl, *R*² is -C1 - C5 alkyl, heterocyclyl, -L-cycloalkyl, -CH₂-aryl and -CH₂-heteroaryl where L is a bond or C1 - C3 alkylene and *R*^{3a} and *R*^{3b} are H. 3-Bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine **30** is reacted with aldehyde or ketone **31**

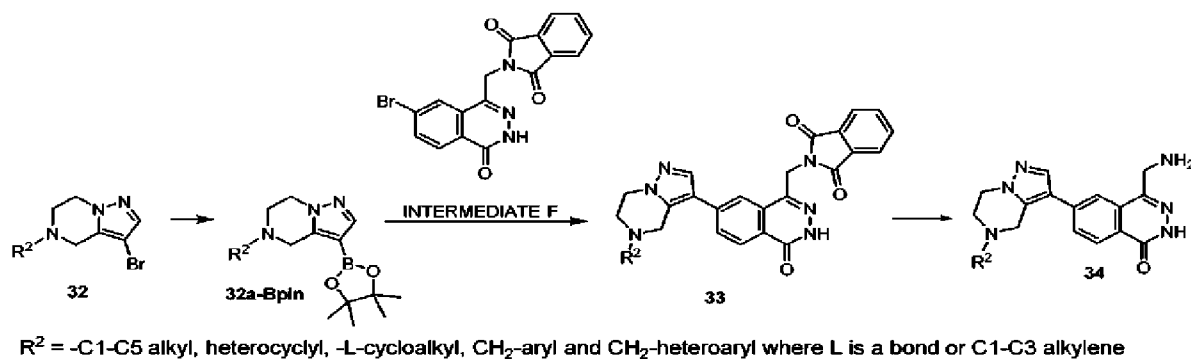
under reductive amination conditions, for example with sodium borohydride in methanol, to form R²-substituted product **32**. Amination product **32** is coupled to boronic ester Intermediate AN under palladium catalyzed cross-coupling, for example Suzuki conditions, furnishing coupling product **33**. Coupling product **33** is then exposed to solvolysis conditions, for example with hydrazine hydrate, to deliver free amine **34** of Formula (I).

GENERAL REACTION SCHEME IV-D



[0153] Compounds of Formula (I) wherein R¹ is aryl or heteroaryl, may be prepared according to General Reaction Scheme IV-D. Compound **94** is an example of Formula (I) wherein R¹ is an appropriately substituted aryl or heteroaryl and R^{3a} and R^{3b} are H. N-Boc boronic ester Intermediate J is coupled to an aryl/heteroaryl-substituted halide **92** under palladium catalyzed cross coupling conditions, for example Suzuki coupling conditions, to generate N-Boc-R¹-substituted coupling product **90**. N-Boc-R¹-substituted coupling product **90** is subjected to acidic conditions to remove the Boc group, for example TFA, to afford R¹-substituted amine **94** of Formula (I).

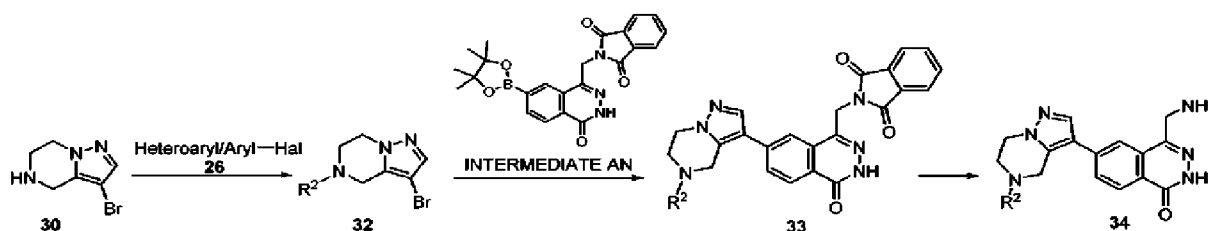
GENERAL REACTION SCHEME IV-E



[0154] Compounds of Formula (I) wherein R¹ is 5-R²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl and R² is -C1 - C5 alkyl, heterocyclyl, -L-cycloalkyl, -CH₂-aryl and -CH₂-heteroaryl where L is a bond or C1 - C3 alkylene, may be prepared according to General

Reaction Scheme IV-E. Compound **34** is an example of Formula (I) wherein R¹ is 5-R²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl, R² is -C1 - C5 alkyl, heterocyclyl, -L-cycloalkyl, -CH₂-aryl and -CH₂-heteroaryl where L is a bond or C1 - C3 alkylene and R^{3a} and R^{3b} are H. 3-Bromo-5-R²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine **32** is borylated, for example with Miyaura conditions, to supply boronate ester **32a-Bpin**. Borylation product **32a-Bpin** is coupled to Intermediate F under palladium catalyzed cross-coupling conditions, for example Suzuki conditions, furnishing coupling product **33a**. Coupling product **33a** is deprotected under acidic conditions, for example TFA, to deliver amine **34a** of Formula (I).

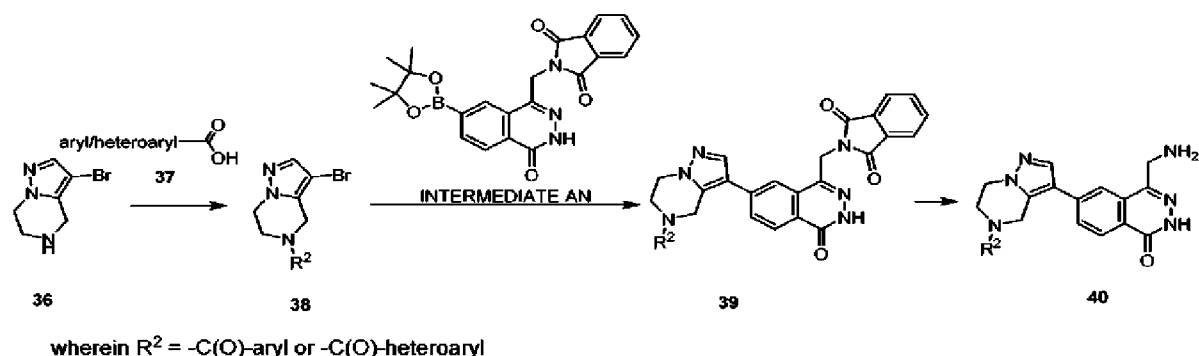
GENERAL REACTION SCHEME IV-F



Wherein R² = aryl or heteroaryl, and Hal = Cl, Br or I

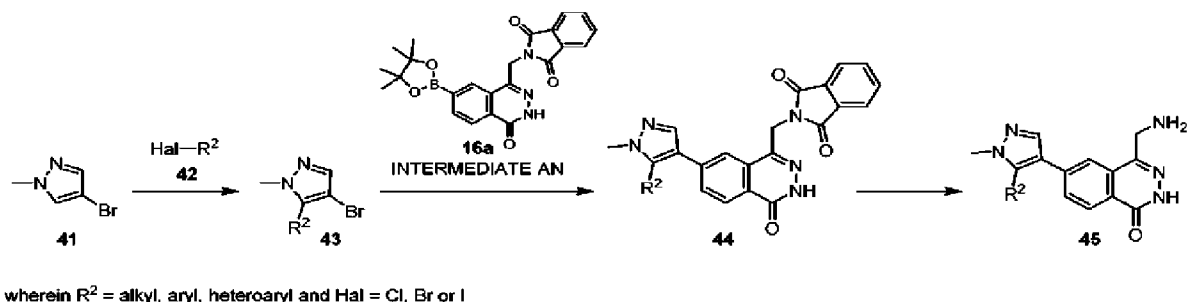
[0155] Compounds of Formula (I) wherein R¹ is 5-R²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl and R² is aryl or heteroaryl, may be prepared according to General Reaction Scheme IV-F. Compound **34** is an example of Formula (I) wherein R¹ is 5-R²-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl, R² is aryl or heteroaryl and R^{3a} and R^{3b} are H. 3-Bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine **30** is reacted with aryl/heteroaryl halide **26**, under copper catalyst mediated Ullman coupling conditions, for example with Cu(I)I, Cs₂CO₃, L-proline in DMF, at elevated temperature, to form amination product **32**. R²-substituted amination product **32** is coupled to Intermediate AN under palladium catalyzed cross-coupling conditions, for example Suzuki conditions, furnishing coupling product **33**. Coupling product **33** is subjected to solvolysis conditions, for example hydrazine hydrate, to deliver amine **34** of Formula (I).

GENERAL REACTION SCHEME IV-G



[0156] Compounds of Formula (I) wherein R^1 is 5- R^2 -6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl and R^2 is $-C(O)-\text{aryl}$ or $-C(O)-\text{heteroaryl}$, may be prepared according to General Reaction Scheme IV-G. Compound 40 is an example of Formula (I) wherein R^1 is 5- R^2 -6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-yl, R^2 is $-C(O)-\text{aryl}$ or $-C(O)-\text{heteroaryl}$ and R^{3a} and R^{3b} are H. 3-Bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine 30 is coupled to carboxylic acid 37 with a coupling reagent, for example 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) with a base such as triethylamine in DMF to form amide 38. Amide 38 is coupled to boronic ester Intermediate AN, under palladium catalyzed cross-coupling conditions, for example the Suzuki coupling, to yield coupling product 39. R^2 -coupling product 39 is subjected to solvolysis conditions, for example with hydrazine monohydrate, to remove the phthalimide moiety and provide amine compound 40 of Formula (I).

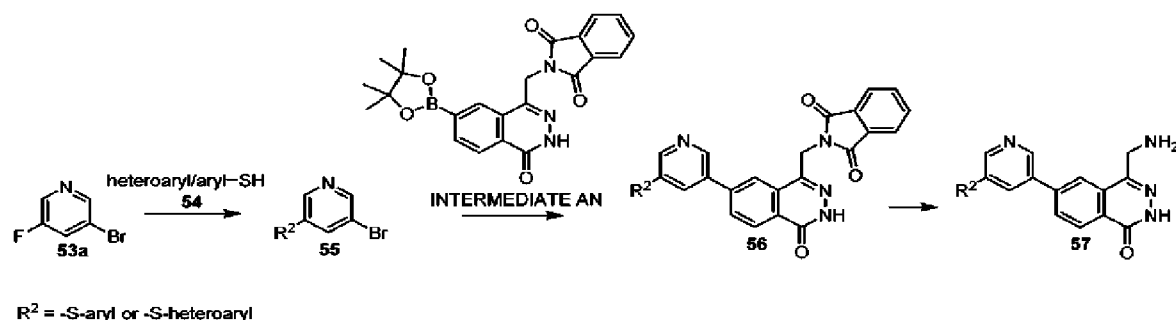
GENERAL REACTION SCHEME IV-H



[0157] Compounds of Formula (I) wherein R^1 is 1-methyl-5- R^2 -1*H*-pyrazole-4-yl and R^2 is alkyl, aryl or heteroaryl, may be prepared according to General Reaction Scheme IV-H. Compound 45 is an example of Formula (I) wherein R^1 is 1-methyl-5- R^2 -1*H*-pyrazole-4-yl, R^2 is alkyl, aryl or heteroaryl and R^{3a} and R^{3b} are H. 4-bromo-1-methyl-1*H*-pyrazole 41 is coupled

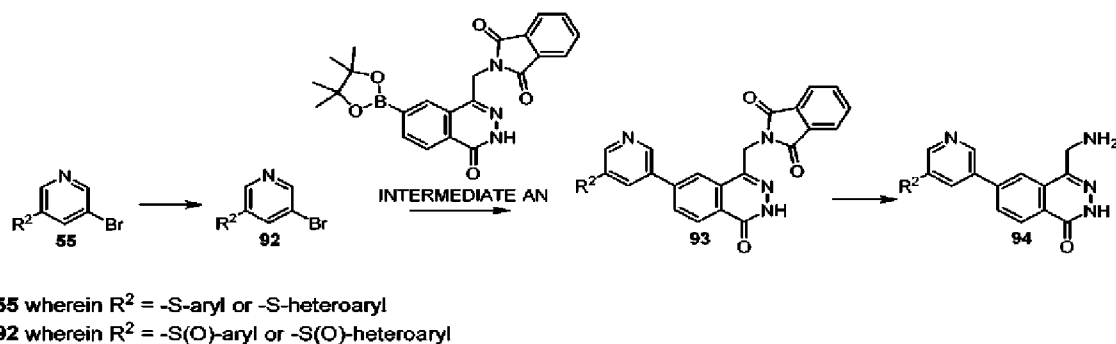
to alkyl/aryl/heteroaryl-substituted halide **42**, for example with palladium acetate, DavePhos, tetrabutylammoniumacetate, pivalic acid in NMP at elevated temperature to furnish R²-substituted-bromopyrazole **43**. R²-substituted-bromopyrazole **43** is coupled to Intermediate AN under palladium-mediated cross coupling conditions, for example Suzuki conditions, to provide R²-substituted coupling product **44**. The coupling product **44** is subjected to solvolysis conditions, for example with hydrazine hydrate to furnish amine **45** of Formula (I).

GENERAL REACTION SCHEME IV-I



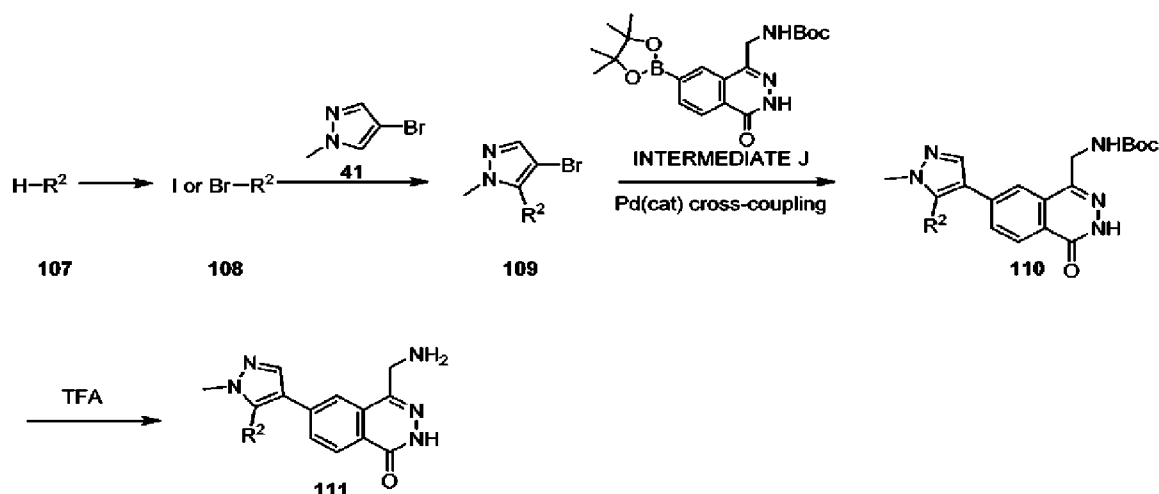
[0158] Compounds of Formula (I) wherein R¹ is pyridyl, R² is -S-aryl or -S-heteroaryl, may be prepared according to General Reaction Scheme IV-I. Compound **57** is an example of Formula (I) wherein R¹ is pyridyl, R² is -S-aryl or -S-heteroaryl and R^{3a} and R^{3b} are H. 3-bromo-5-fluoropyridine **53a** is subjected to S_NAr substitution conditions, for example sodium aryl/heteroaryl thiolate **54**, NaH in DMF at elevated temperature, to provide 3-bromo-5-(aryl/heteroarylthio)pyridine **55**. 3-bromo-5-(aryl/heteroarylthio)pyridine **55** is coupled with boronic ester Intermediate AN under palladium cross coupling conditions, for example Suzuki conditions, to furnish R²-pyridyl-cross coupling product **56**. R²-pyridyl-cross coupling product **56** is subjected to solvolysis conditions, with for example hydrazine hydrate, to produce amine **57** of Formula (I).

GENERAL REACTION SCHEME IV-J



[0159] Compounds of Formula (I) wherein R¹ is pyridyl, R² is -S(O)-aryl or -S(O)-heteroaryl, may be prepared according to General Reaction Scheme IV-J. Compound **94** is an example of Formula (I) wherein R¹ is pyridyl, R² is -S(O)-aryl or -S(O)-heteroaryl and R^{3a} and R^{3b} are H. 3-bromo-5-(R²-thio)pyridine **55** is subjected to oxidation conditions, for example mCPBA in dichloromethane at ambient temperature, to afford 3-bromo-5-(R²-sulfinyl)pyridine **92**. 3-bromo-5-(R²-sulfinyl)pyridine **92** is coupled with boronic ester intermediate AN under palladium catalyzed cross-coupling conditions, for example Suzuki conditions, to provide R²-substituted sulfinylpyridyl product **93**. R²-substituted sulfinylpyridyl product **93** is subjected to solvolysis conditions, for example with hydrazine hydrate, to procure the R²-substituted sulfinylpyridyl amine **94** of Formula (I).

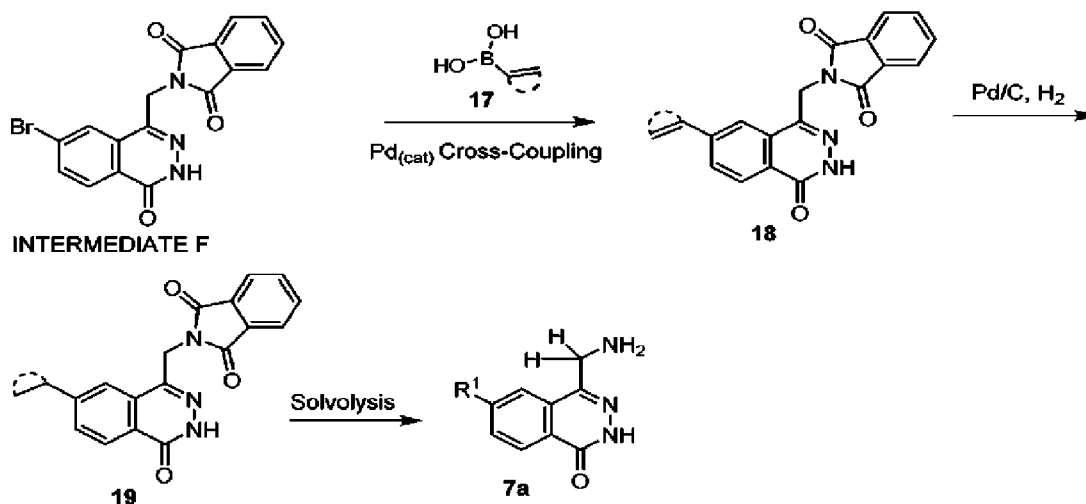
GENERAL REACTION SCHEME IV-K



[0160] Compounds of Formula (I) wherein R¹ is 1-methyl-5-R²-1H-pyrazole-4-yl and R² is alkyl, aryl or heteroaryl, may be prepared according to General Reaction Scheme IV-K. Compound **111** is an example of Formula (I) wherein R¹ is 1-methyl-5-R²-1H-pyrazole-4-yl, R² is alkyl, aryl or heteroaryl and R^{3a} and R^{3b} are H. H-R² **107** is halogenated, for example with a halogenating agent such as N-bromosuccinimide or N-chlorosuccinimide under palladium catalyzed conditions such as palladium acetate in the presence of an acid such as p-toluenesulfonic acid in a solvent such as dichloroethane under elevated temperature for example 70°C to give halide **108**. 4-bromo-1-methyl-1H-pyrazole **41** is coupled to alkyl/aryl/heteroaryl-substituted halide **108**, for example with palladium acetate, DavePhos, tetrabutylammoniumacetate, pivalic acid in NMP at elevated temperature to furnish R²-substituted-bromopyrazole **109**. R²-substituted-bromopyrazole **109** is coupled to Intermediate

J under palladium-mediated cross coupling conditions, for example Suzuki conditions, to provide N-Boc-R²-substituted coupling product **110**. The coupling product **110** is subjected to acidic conditions to remove the Boc group, for example TFA, to afford R²-substituted amine **111** of Formula (I).

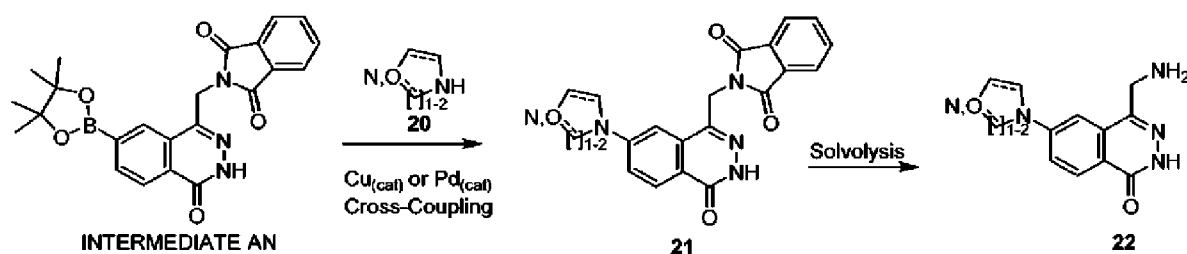
GENERAL REACTION SCHEME V



R¹ = cycloalkyl or heterocyclyl

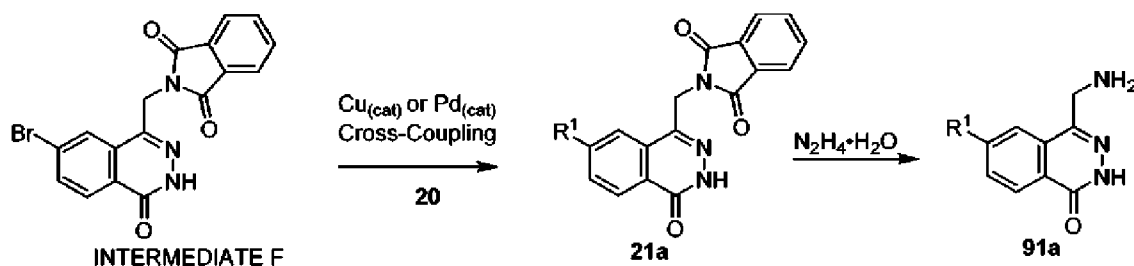
[0161] Compounds of Formula (I) wherein R¹ is cycloalkyl or heterocyclyl, may be prepared according to General Reaction Scheme V. Compound **7a** is an example of Formula (I) wherein R¹ is cycloalkyl or heterocyclyl and R^{3a} and R^{3b} are H. 2-((7-bromo-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione Intermediate **F** is coupled to a 4-6 membered ring olefin boronic acid **17** under palladium catalyzed coupling conditions, for example Suzuki coupling conditions to provide the appropriate olefinic coupling product **18**. The olefin coupling product **18** is then subjected to hydrogenation conditions, for example Pd/C and H₂, to furnish the appropriate hydrogenation product **19**. The hydrogenation product is then subjected to hydrazine solvolysis conditions, for example with hydrazine hydrate to provide the primary amine compound **7a** of Formula (I).

GENERAL REACTION SCHEME VI-A



[0162] Compounds of Formula (I) wherein R¹ is N-linked heteroaryl or N-linked heterocyclyl, may be prepared according to General Reaction Scheme VI-A. Compound **22** is an example of Formula (I) wherein R¹ is N-linked heteroaryl or N-linked heterocyclyl and R^{3a} and R^{3b} are H. Boronic ester intermediate **AN**, is subjected to metal catalyzed cross-coupling conditions, for example Ullman, Buchwald-Hartwig or Chan-Lam conditions with a nitrogen containing heterocyclyl or a nitrogen containing heteroaryl **20** to provide the appropriate N-coupled product **21**. This N-coupled product **21** is subjected to solvolysis conditions, for example with hydrazine hydrate to remove the phthalimide to furnish the desired primary amine **22** of Formula (I).

GENERAL REACTION SCHEME VI-B

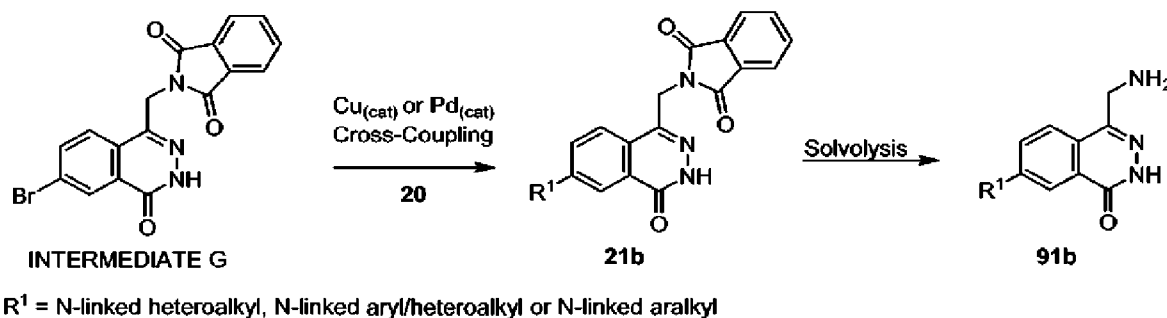


R¹ = N-linked heteroalkyl, N-linked aryl/heteroalkyl or N-linked aralkyl

[0163] Compounds of Formula (I) wherein R¹ is N-linked heteroaryl or N-linked heterocyclyl, may be prepared according to General Reaction Scheme VI-B. Compound **23** is an example of Formula (I) wherein R¹ is N-linked heteroaryl or N-linked heterocyclyl and R^{3a} and R^{3b} are H. 2-((7-bromo-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione Intermediate **F**, is subjected to metal catalyzed cross-coupling conditions, for example Ullman, Buchwald-Hartwig or Chan-Lam conditions with a nitrogen containing heterocyclyl or nitrogen containing heteroaryl **20** to provide the appropriate N-coupled product **21a**. This

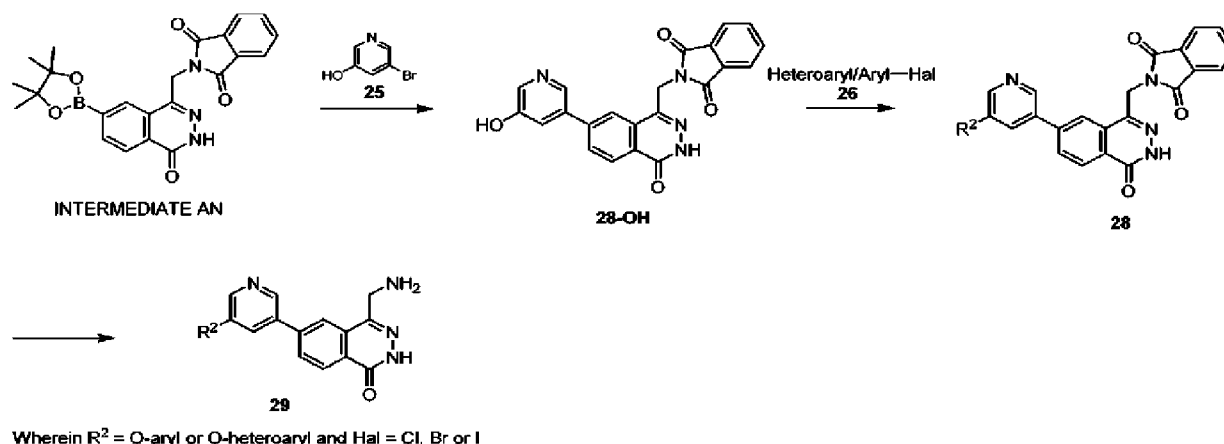
N-coupled product **21a** is then subjected to solvolysis conditions, for example with hydrazine hydrate to furnish the desired primary amine **91a** of Formula (I).

GENERAL REACTION SCHEME VI-C



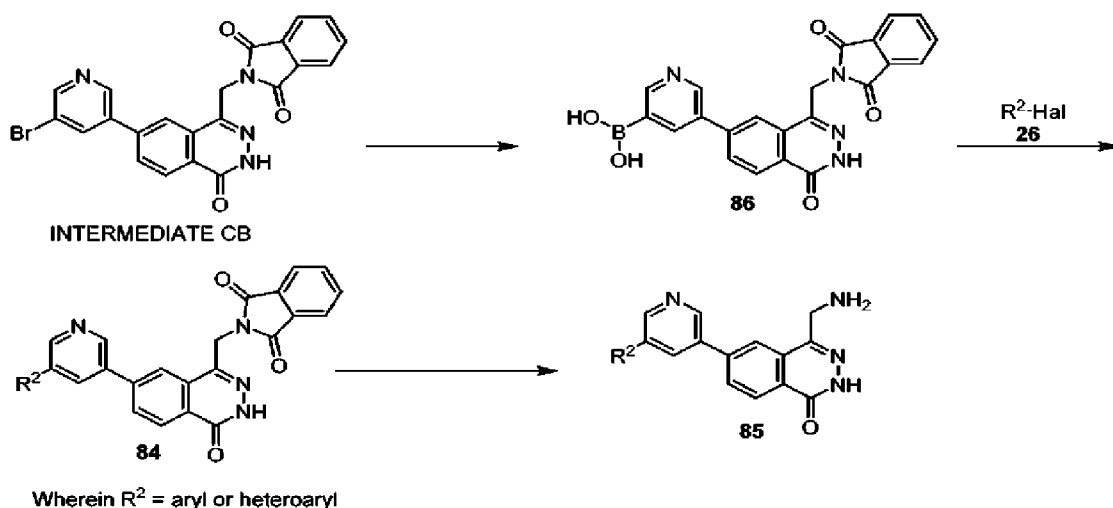
[0164] Compounds of Formula (I) wherein R¹ is N-linked heteroalkyl, N-linked arylheteroalkyl or N-linked aralkyl, may be prepared according to General Reaction Scheme VI-C. Compound **24** is an example of Formula I wherein R¹ is N-linked heteroalkyl, N-linked arylheteroalkyl or N-linked aralkyl and R^{3a} and R^{3b} are H. 2-((6-bromo-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione intermediate **F**, is subject to metal catalyzed cross-coupling conditions, for example Ullman, Buchwald-Hartwig or Chan-Lam conditions with an heteroalkyl/arylheteroalkyl/aralkyl amine **20** to provide the appropriate N-coupled product **21b**. This N-coupled product **21b** is then subject to solvolysis conditions, for example with hydrazine hydrate to furnish the desired R¹ substituted product **91b** of Formula (I).

GENERAL REACTION SCHEME VII



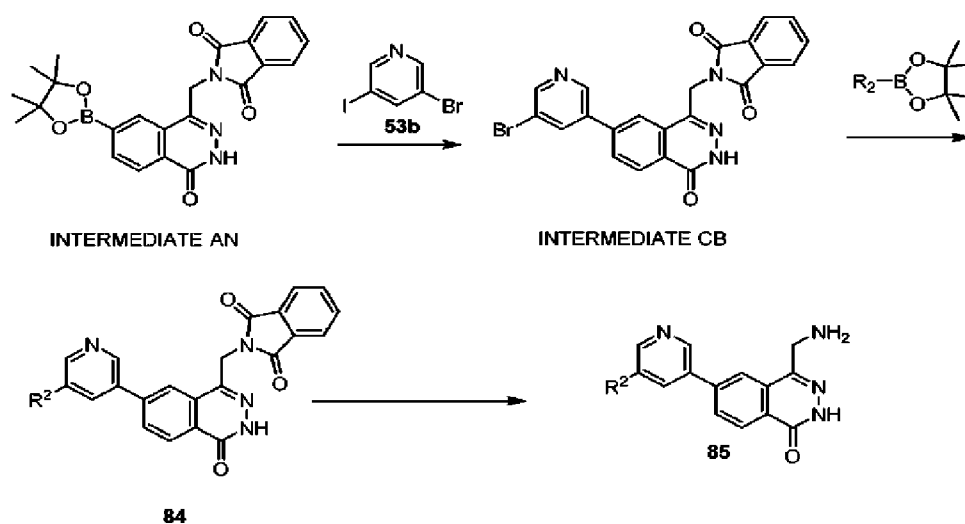
[0165] Compounds of Formula (I) wherein R¹ is pyridyl and R² is O-aryl or O-heteroaryl, may be prepared according to General Reaction Scheme VII. Compound **29** is an example of Formula (I) wherein R¹ is pyridyl, R² is O-aryl or O-heteroaryl and R^{3a} and R^{3b} are H. 3-bromo-5-hydroxypyridine **25** is coupled to boronic ester Intermediate AN under palladium catalyzed cross coupling conditions, for example the Suzuki coupling conditions Pd(dppf)Cl₂, NaHCO₃, dioxane/water at 80°C, to generate coupling product **28-OH**. Coupling product **28-OH** was subjected to S_NAr reaction conditions for example K₂CO₃ in DMF at 110°C with R²-substituted aryl/heteroaryl halide **26**, to furnish R²-substituted aryl/heteroaryl pyridyl ether **28**. R²-substituted aryl/heteroaryl pyridyl ether **28** was subjected to solvolysis conditions, for example hydrazine hydrate to furnish free amine **29** of Formula (I).

GENERAL REACTION SCHEME VIII-A



[0166] Compounds of Formula (I) wherein R¹ is pyridyl and R² is aryl or heteroaryl, may be prepared according to General Reaction Scheme VIII-A. Compound **85** is an example of Formula (I) wherein R¹ is pyridyl, R² is aryl or heteroaryl and R^{3a} and R^{3b} are H. Intermediate CB is borylated under Miyaura conditions, for example with bis(pinacolato)diboron, Pd(dppf)Cl₂, KOAc in dioxane at elevated temperature to provide boronic acid **86**. Boronic acid **86** is coupled with R² halide **26** under palladium catalyzed cross coupling conditions, for example Suzuki conditions, to yield R²-pyridyl coupling product **84**. R²-pyridyl coupling product **84** is subjected to solvolysis conditions, for example with hydrazine hydrate, to provide primary amine **85** of Formula (I).

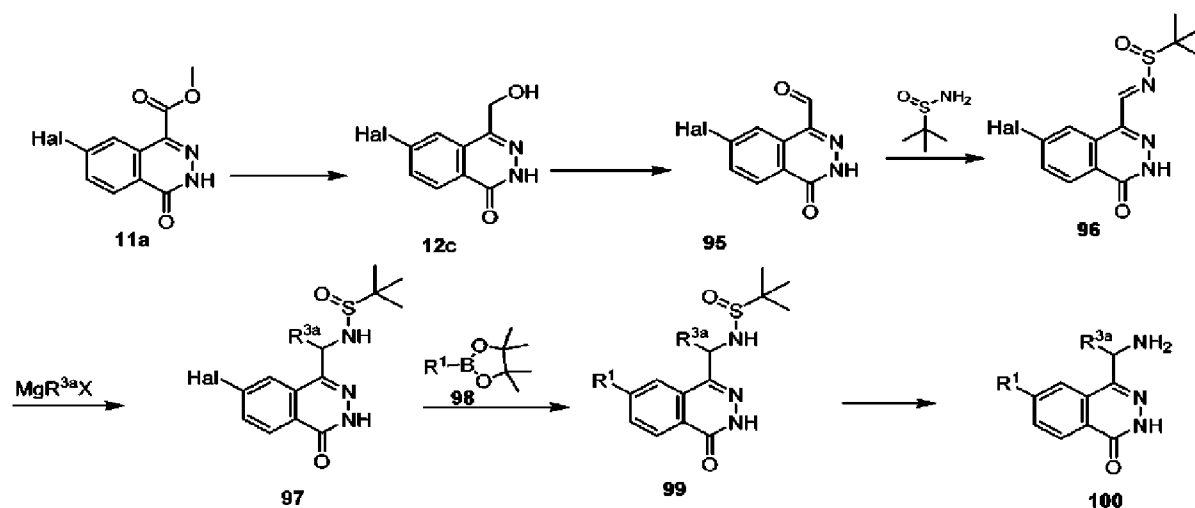
GENERAL REACTION SCHEME VIII-B



wherein R^2 = aryl or heteroaryl

[0167] Compounds of Formula (I) wherein R^1 is pyridyl and R^2 is aryl or heteroaryl, may be prepared according to General Reaction Scheme VIII-B. Compound **85** is an example of Formula (I) wherein R^1 is pyridyl, R^2 is aryl or heteroaryl and R^{3a} and R^{3b} are H. Intermediate AN is coupled to 3-bromo-5-iodopyridine **53b** under palladium catalyzed cross coupling conditions, for example Suzuki conditions, to give 3-bromo-pyridyl coupling product Intermediate CB. Intermediate CB is then coupled to aryl/heteroaryl-substituted boronic ester under palladium catalyzed cross-coupling conditions, for example Suzuki coupling conditions, to provide R^2 -substituted pyridyl coupling product **84**. Coupling product **84** undergoes solvolysis, for example with hydrazine hydrate, to provide primary amine **85** of Formula (I).

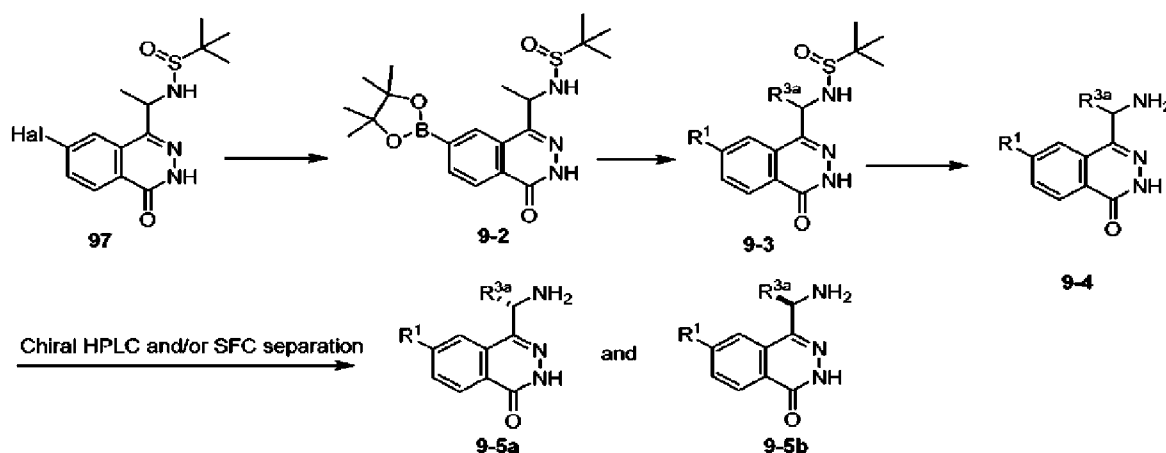
GENERAL REACTION SCHEME IX-A



Wherein R^1 = aryl/heteroaryl, R^{3a} = alkyl and Hal = Cl, Br or I

[0168] Compounds of Formula (I), wherein R^1 is aryl or heteroaryl, R^{3a} is alkyl and R^{3b} is H, may be prepared according to General Reaction Scheme IX-A. Compound **100** is an example of Formula (I) wherein R^1 is aryl or heteroaryl, R^{3a} is alkyl and R^{3b} is H. Methyl 7-halo-4-oxo-3,4-dihydrophthalazine-1-carboxylate **11a** is reduced using a hydride reducing conditions, for example sodium borohydride, CaCl_2 in methanol at 0°C , to afford primary alcohol 6-halo-4-(hydroxymethyl)phthalazin-1(2H)-one **12a**. 6-halo-4-(hydroxymethyl)phthalazin-1(2H)-one **12a** is reacted with an oxidant, for example MnO_2 in dichloroethane to furnish 7-halo-4-oxo-3,4-dihydrophthalazine-1-carbaldehyde **95**. 7-halo-4-oxo-3,4-dihydrophthalazine-1-carbaldehyde **95** is converted to the sulfonamide compound **96** by for example, adding *t*-butanesulfonamide, titanium tetra-*iso*-propoxide in THF and heating to 60°C for 12 hours. *t*-Butyl sulfonamide **96** is then reacted with alkylmagnesium halide in THF at -78°C to generate methyl sulfonamide **97**. Methyl sulfonamide **97** is coupled to an appropriate R^1 -substituted boronic ester under palladium catalyzed cross coupling conditions, for example Suzuki conditions, to supply R^1 -substituted coupling product **99**. R^1 -substituted coupling product **99** is desulfinylated under acidic conditions, for example HCl /dioxane to furnish R^1 -substituted primary amine **100** of Formula (I).

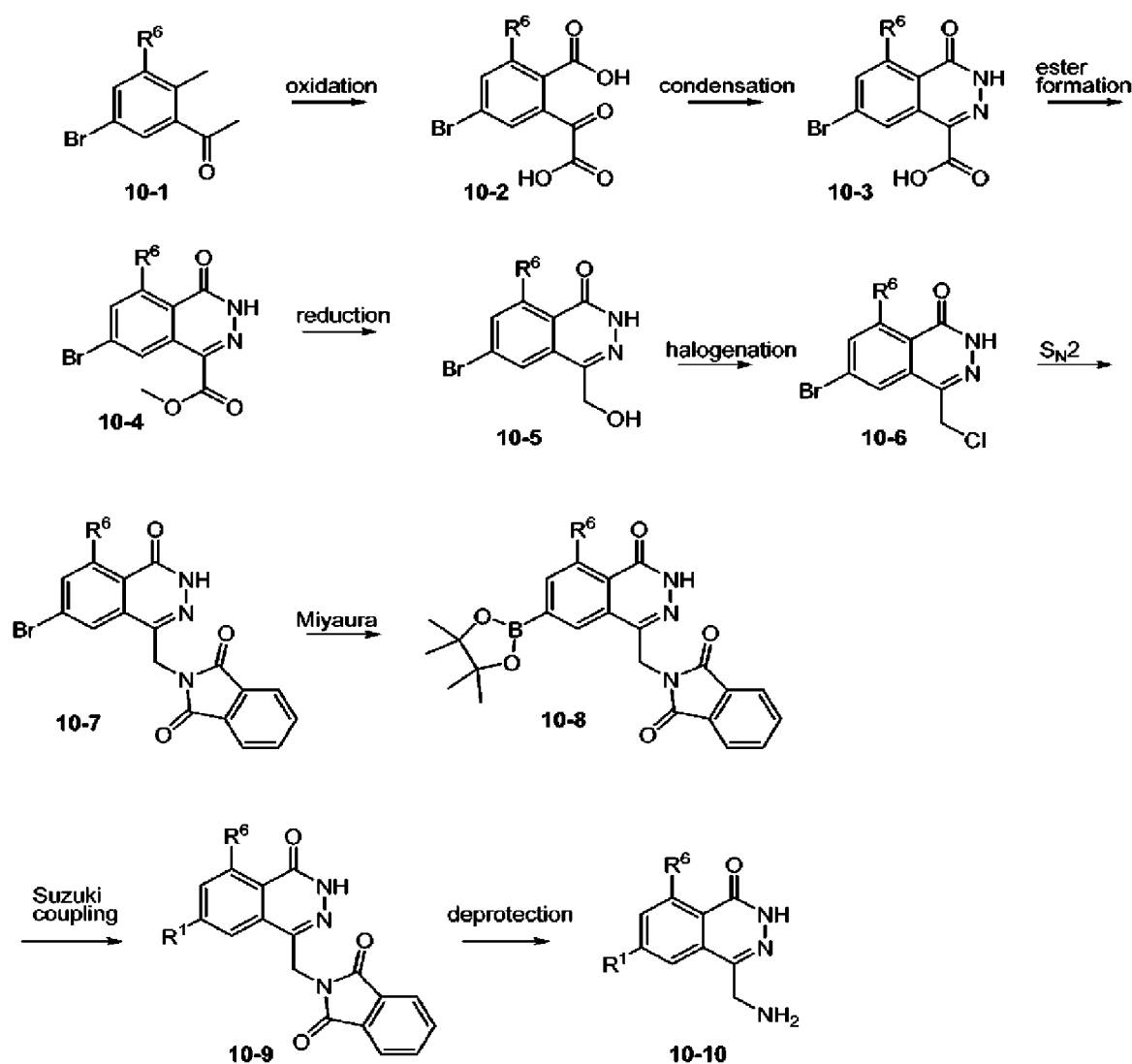
GENERAL REACTION SCHEME IX-B



wherein R¹ = aryl/heteroaryl R^{3a} = alkyl and Hal = Cl, Br or I

[0169] Compounds of Formula (I), wherein R¹ is aryl or heteroaryl, R^{3a} is alkyl and R^{3b} is H, may be prepared according to General Reaction Scheme IX-B. Compounds 9-5a and 9-5b are examples of Formula (I) wherein R¹ is aryl or heteroaryl, R^{3a} is alkyl and R^{3b} is H. t-Butyl sulfonamide intermediate 97 is borylated under Miyaura conditions, for example with bis(pinacolato)diboron, Pd(dppf)Cl₂, KOAc in dioxane at elevated temperature to provide boronic ester 9-2 which is then reacted coupled to an appropriate R¹-substituted halide under palladium catalyzed cross coupling conditions, for example Suzuki conditions, to supply R¹-substituted coupling product 9-3. R¹-substituted coupling product 9-3 is desulfinylated under acidic conditions, for example HCl/dioxane to furnish R¹-substituted primary amine 9-4 of Formula (I). The racemic mixture of 9-4 is then separated into the corresponding pure enantiomers via chiral prep HPLC and or chiral SFC to give chiral amines 9-5a and 9-5b examples of compounds of Formula (I).

GENERAL REACTION SCHEME X

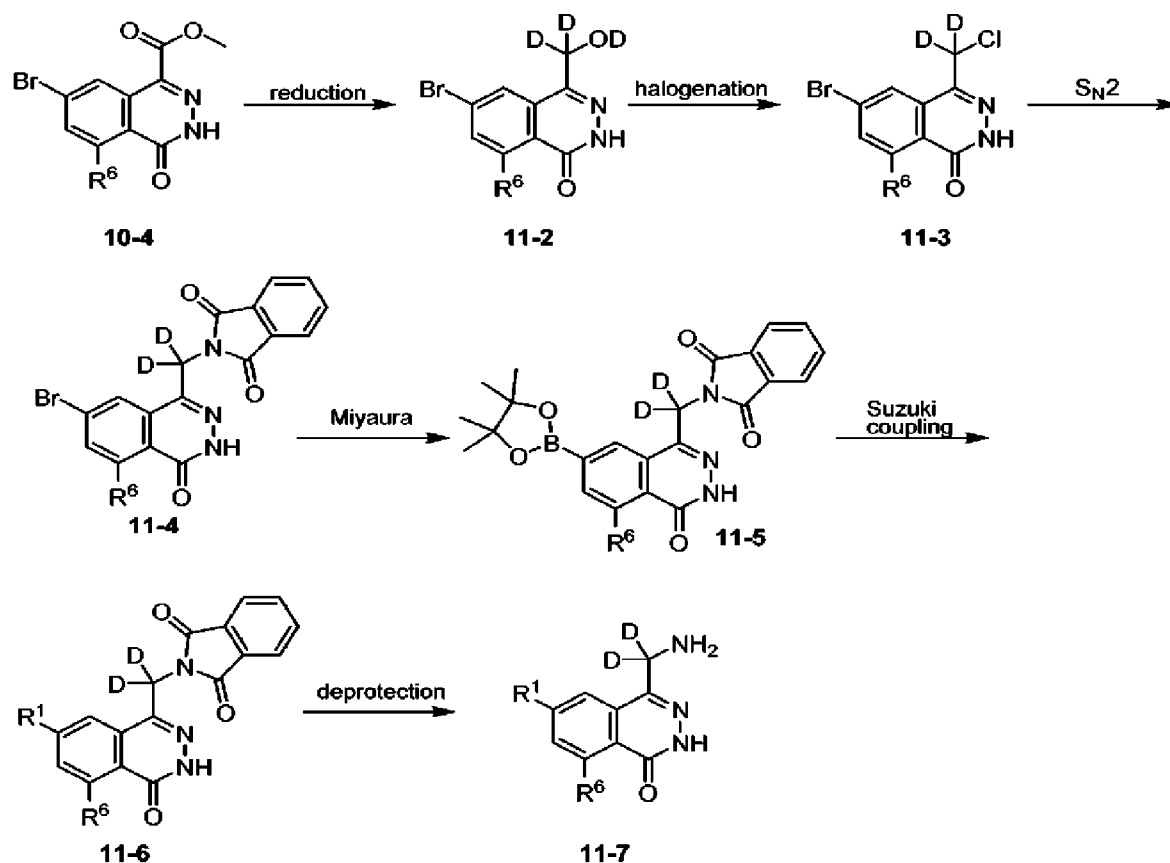


wherein R¹ = aryl/heteroaryl and R⁶ = H, halogen, C1-C3 alkyl or alkoxy

[0170] Compounds of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl, may be prepared according to General Reaction Scheme X. Compound 10-10 is an example of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl, R^{3a} and R^{3b} are H and R⁶ is hydrogen, halogen, C1-C3 alkyl or alkoxy. 1-(5-bromo-2-methyl-3-substituted phenyl)ethanone 10-1 is treated with an oxidant, for example KMnO₄ in water at 50°C to furnish 4-bromo-2-(carboxycarbonyl)-6-substituted-benzoic acid 10-2. Condensation of 10-2, for example with hydrazine hydrate in ethanol at elevated temperature, yields 7-bromo-4-oxo-3,4-dihydrophthalazine-5-substituted-1-carboxylic acid 10-3 which is then esterified with acid and alcohol, for example sulfuric acid and methanol to give ester 10-4. Methyl 7-bromo-4-

oxo-3,4-dihydrophthalazine-5-substituted-1-carboxylate **10-4** is reduced via hydride reduction, for example with sodium borohydride and CaCl_2 in methanol, to afford the 6-bromo-4-(hydroxymethyl)-8-substituted-phthalazin-1(2H)-one **10-5**, which is then treated with halogenating agent, for example thionyl chloride for 12 hours to provide 6-halo-4-(chloromethyl)-8-substituted-phthalazin-1(2H)-one **10-6**. Nucleophilic $\text{S}_{\text{N}}2$ displacement of **10-6** with a nitrogen nucleophile for example, potassium phthalimide in DMF at elevated temperature furnishes **10-7** which is borylated, for example with Miyaura conditions, to give boronate ester **10-8**. Palladium-mediated cross coupling conditions, for example Suzuki conditions, with boronic ester **10-8** and aryl/heteroaryl/heterocyclyl/alkyl halides provides phthalazinone coupling product **10-9**. The phthalimide protecting group of **10-9** is removed under solvolysis conditions, for example with hydrazine hydrate in ethanol to furnish the desired compound **10-10** of Formula (I).

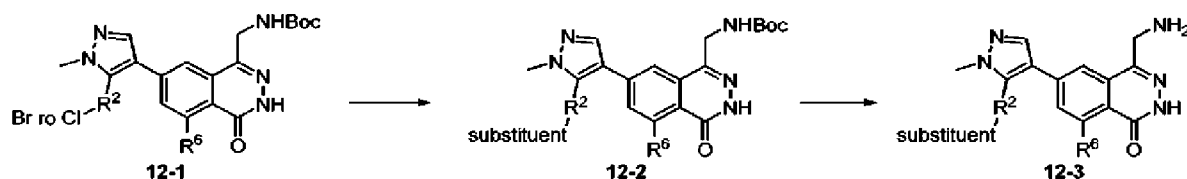
GENERAL REACTION SCHEME XI



wherein R^1 = aryl/heteroaryl, R^{3a} , R^{3b} are D and R^6 = H, halogen, C1-C3 alkyl or alkoxy

[0171] Compounds of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl, may be prepared according to General Reaction Scheme XI. Compound **11-7** is an example of Formula (I) wherein R¹ is aryl, heteroaryl, heterocyclyl or alkyl, R^{3a} and R^{3b} are D and R⁶ is hydrogen, halogen, C1-C3 alkyl or alkoxy. Methyl 7-bromo-4-oxo-3,4-dihydrophthalazine-5-substituted-1-carboxylate **10-4** is reduced via deuteride reduction, for example with sodium borodeuteride and CaCl₂ in methanol-d₄, to afford the 6-bromo-4-((hydroxy-d)methyl-d₂)-8-substituted-phthalazin-1(2H)-one **11-2**, which is then treated with halogenating agent, for example thionyl chloride for 12 hours to provide 6-bromo-4-(chloromethyl-d₂)-8-substituted-phthalazin-1(2H)-one **11-3**. Nucleophilic S_N2 displacement of **11-3** with a nitrogen nucleophile for example, potassium phthalimide in DMF at elevated temperature furnishes **11-4** which is borylated, for example with Miyaura conditions, to give boronate ester **11-5**. Palladium-mediated cross coupling conditions, for example Suzuki conditions, with boronic ester **11-5** and aryl/heteroaryl/heterocyclyl/alkyl halides provides phthalazinone coupling product **11-6**. The phthalimide protecting group of **11-6** is removed under solvolysis conditions, for example with hydrazine hydrate in ethanol to furnish the desired compound **11-7** of Formula (I).

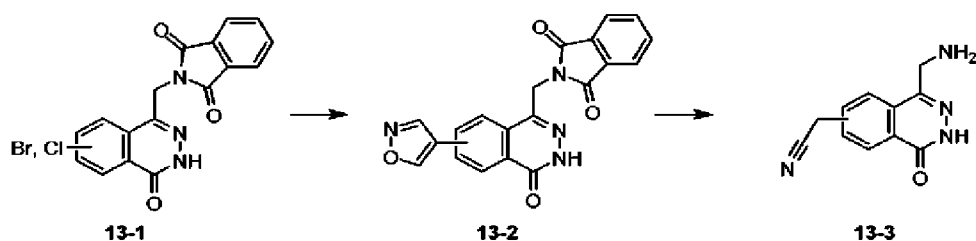
GENERAL REACTION SCHEME XII



wherein R² = aryl/heteroaryl and R⁶ = H, halogen, C1-C3 alkyl or alkoxy

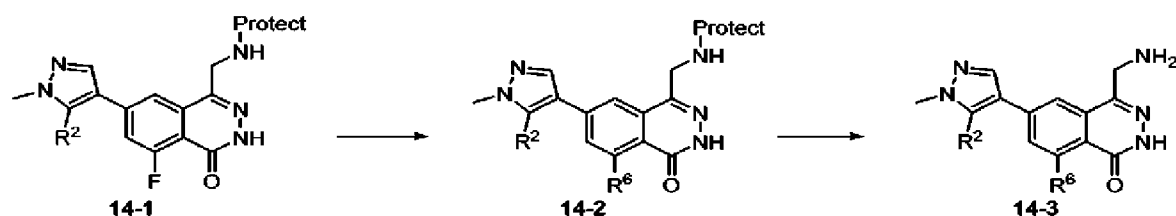
[0172] Compounds of Formula (I) wherein R² is aryl or heteroaryl, may be prepared according to General Reaction Scheme XII. Compound **12-3** is an example of Formula (I) wherein R² is aryl or heteroaryl, R^{3a} and R^{3b} are H, R⁶ is hydrogen, halogen, C1-C3 alkyl or alkoxy and substituent is alkyl, aryl or heteroaryl. Bromo or chloro compound **12-1** is subjected to palladium-mediated cross coupling conditions, for example Suzuki conditions, with an alkyl/aryl/heteroaryl boronic acid/ester to give substituent coupled product **12-2**. The BOC group is then removed with acidic conditions, for example TFA, to afford R²-substituted amine **12-3** of Formula (I).

GENERAL REACTION SCHEME XIII



[0173] Compounds of Formula (I) wherein R¹ is alkyl-cyano, may be prepared according to General Reaction Scheme XIII. Compound 13-3 is an example of Formula (I) wherein R¹ is -CH₂CN. Bromo or chloro compound 13-1 is subjected to palladium-mediated cross coupling conditions, for example Suzuki conditions, with an isoxazole boronic acid/ester to give substituent coupled product 13-2. The isoxazole is then subjected to hydrazine hydrate in an alcoholic solvent such as ethanol at elevated temperature followed by acidic work up, for example with HCl at pH 1 to give nitrile product 13-3 of Formula (I).

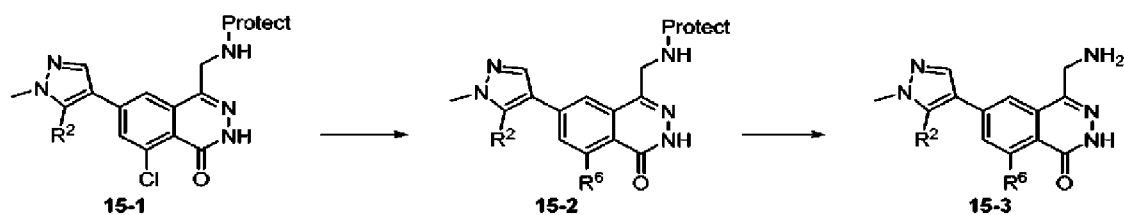
GENERAL REACTION SCHEME XIV



wherein R² = aryl/heteroaryl and R⁶ = alkoxy

[0174] Compounds of Formula (I) wherein R² is aryl or heteroaryl and R⁶ is alkoxy may be prepared according to General Reaction Scheme XIV. Compound 14-3 is an example of Formula (I) wherein R² is aryl or heteroaryl, and R⁶ is alkoxy. Fluoro compound 14-1 with the amine suitably protected with for example, a BOC group or phthalimide group is subjected to aromatic S_N2 conditions with -F as the leaving group and the corresponding oxy anion as the nucleophile. For example, with a sodium alkyl oxide in a polar solvent with heat to give substituent substituted product 14-2. The protecting group is then removed under appropriate conditions. For example, the BOC is removed under acidic conditions such as HCl or TFA in dioxane or the phthalimide group is removed under basic nucleophilic conditions such as hydrazine hydrate in ethanol with heat to afford R⁶-substituted amine 14-3 of Formula (I).

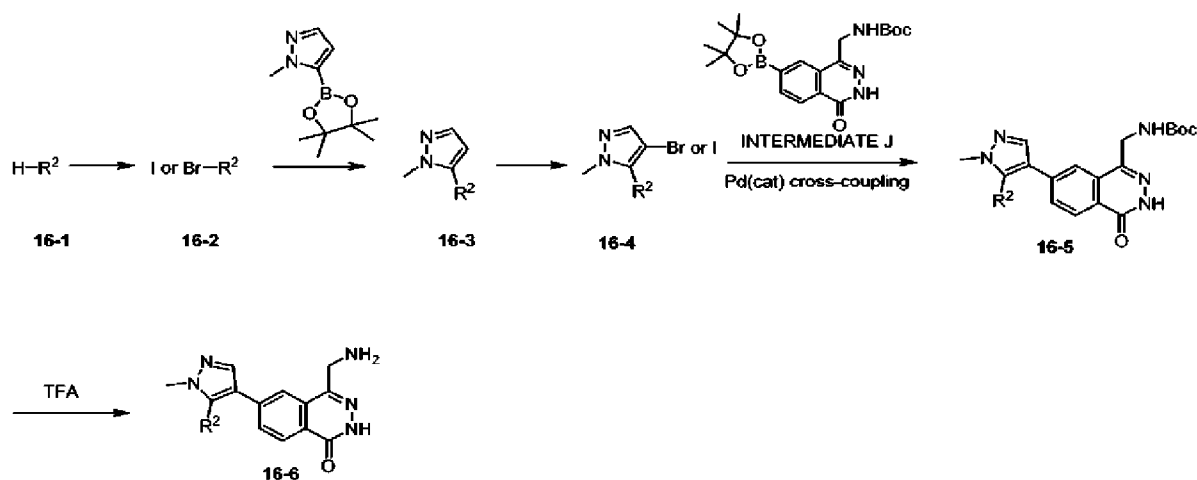
GENERAL REACTION SCHEME XV



wherein R² = aryl/heteroaryl and R⁶ = C1-C3 alkyl

[0175] Compounds of Formula (I) wherein R² is aryl or heteroaryl and R⁶ is C1-C3 alkyl may be prepared according to General Reaction Scheme XV. Compound 15-3 is an example of Formula (I) wherein R² is aryl or heteroaryl, and R⁶ is C1-C3 alkyl. Chloro compound 15-1 with the amine suitably protected with for example, a BOC group or phthalimide group, is coupled to the appropriate C1-C3 trialkylborane under palladium catalyzed cross coupling conditions, for example Suzuki-Miyaura coupling conditions, to supply the corresponding R⁶-substituted coupling product 15-2. The protecting group is then removed under appropriate conditions. For example, the BOC is removed under acidic conditions such as HCl in dioxane or TFA in dioxane and the phthalimide group is removed under basic nucleophilic conditions such as hydrazine hydrate in ethanol with heat to afford R⁶-substituted amine 15-3 of Formula (I).

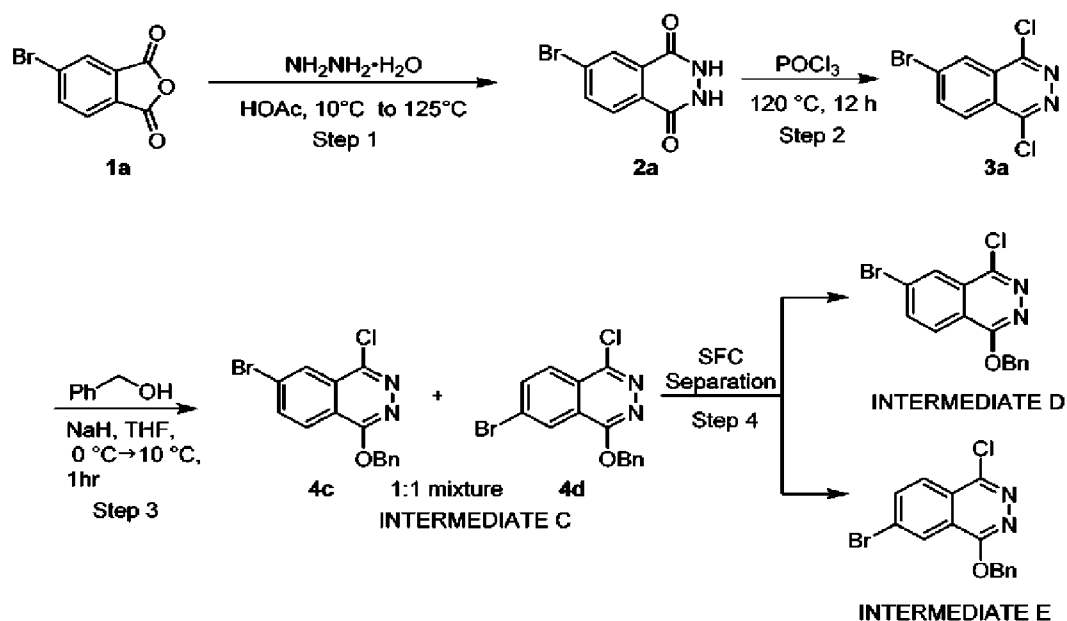
GENERAL REACTION SCHEME XVI



[0176] Compounds of Formula (I) wherein R¹ is 1-methyl-5-R²-1H-pyrazole-4-yl and R² is alkyl, aryl or heteroaryl, may be prepared according to General Reaction Scheme XVI. Compound 16-6 is an example of Formula (I) wherein R¹ is 1-methyl-5-R²-1H-pyrazole-4-yl,

R^2 is alkyl, aryl or heteroaryl and R^{3a} and R^{3b} are H. H- R^2 **16-1** is halogenated, for example with a halogenating agent such N-bromosuccinimide or N-iodosuccinimide under palladium catalyzed conditions such as palladium acetate in the presence of an acid such as p-toluenesulfonic acid in a solvent such as dichloroethane under elevated temperature for example 70 °C to give halide **16-2**. Bromo or iodo compound **16-2** is subjected to palladium-mediated cross coupling conditions, for example Suzuki conditions, with 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give coupled product **16-3**. 1-methyl-5- R^2 -1H-pyrazole **16-3** is halogenated for example with a halogenating agent such N-bromosuccinimide or N-iodosuccinimide in a polar solvent such as acetonitrile to give 4-halo-1-methyl-5- R^2 -1H-pyrazole compound **16-4**. 4-bromo-1-methyl-5- R^2 -1H-pyrazole **16-4** is coupled to Intermediate J under palladium-mediated cross coupling conditions, for example Suzuki conditions, to provide N-Boc- R^2 -substituted coupling product **16-5**. The coupling product **16-5** is subjected to acidic conditions to remove the Boc group, for example TFA, to afford R^2 -substituted amine **16-6** of Formula (I).

INTERMEDIATES C, D and E



[0177] **Step 1:** A mixture of 5-bromoisobenzofuran-1,3-dione **1a** (55.0 g, 242 mmol, 1.00 *eq.*) and acetic acid (165 mL) was stirred at 125°C for 1 hour. After such time the mixture was cooled to 10°C and hydrazine hydrate (12.7 g, 254 mmol, 12.4 mL, 1.05 *eq.*) was added

dropwise, resulting in the formation of a thick white precipitate. Additional acetic acid (55 mL) was added and the mixture stirred at 125 °C for a further 30 mins. After such time the mixture was cooled, diluted with acetic acid (150 mL) and filtered. The filter cake was washed with acetic acid (50 mL $\times$ 3), dried and then dissolved in a 5% (w/w) sodium hydroxide solution (800 mL). The solution was acidified with acetic acid (200 mL) to give a thick white precipitate which was filtered. The filter cake was washed with water (50 mL $\times$ 3) followed by methanol then dried in vacuo to give 6-bromo-2,3-dihydrophthalazine-1,4-dione **2a** (45.6 g, crude) as a white solid. This solid was then used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.17 (d, *J* = 2.0 Hz, 1H), 8.01 - 7.97 (m, 1H), 7.95 - 7.89 (m, 1H).

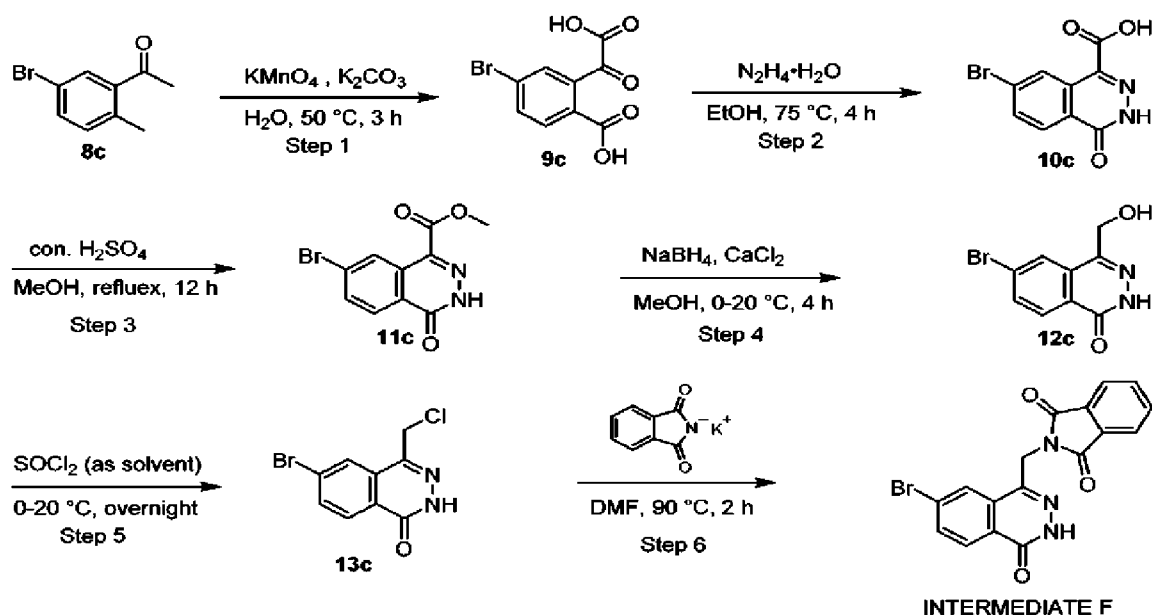
[0178] **Step 2:** A solution of 6-bromo-2,3-dihydrophthalazine-1,4-dione **2a** (20.0 g, crude) in phosphorus oxychloride (330 g, 2.15 mol, 200 mL) was stirred at 120 °C for 12 hours. After such time the reaction mixture was concentrated under reduced pressure and the residue dissolved in dichloromethane (150 mL) and added dropwise to ice-water. The mixture was then extracted with dichloromethane (300 mL $\times$ 3) and the combined organic layers were washed with sodium bicarbonate aqueous solution (200 mL $\times$ 5), brine (200 mL $\times$ 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6-bromo-1,4-dichloro-phthalazine **3a** (14.5 g, crude) as a yellow solid. This solid was then used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ = 8.49 (d, *J* = 1.2 Hz, 1H), 8.23 - 8.15 (m, 2H).

[0179] **Step 3:** A solution of benzyl alcohol (4.59 g, 42.4 mmol, 4.41 mL) and sodium hydride (3.77 g, 94.3 mmol, 60% dispersion in mineral oil) in THF (30 mL) was stirred at 0 °C for 0.5 hour. The mixture was then added dropwise to a solution of 6-bromo-1,4-dichloro-phthalazine **3a** (13.1 g, crude) in THF (80 mL) at 0 °C. The reaction mixture was warmed to 10 °C and stirred at 10 °C for 1 hour. After such time the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (150 mL $\times$ 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-25%) to give Intermediate C, a 1:1 mixture of 4-benzyloxy-7-bromo-1-chloro-phthalazine **4c** and 4-benzyloxy-6-bromo-1-chloro-phthalazine **4d** (9.79 g, 28.0 mmol, 66% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.39 (d, *J* = 1.2 Hz, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.17 - 8.10 (m, 1H), 8.08 - 8.05 (m, 1H), 8.04 (d, *J* =

2.0 Hz, 1H), 8.00 (dt, $J = 1.6, 8.4$ Hz, 1H), 7.59 - 7.53 (m, 4H), 7.47 - 7.36 (m, 6H), 5.70 (s, 4H).

[0180] **Step 4:** The regioisomers of Intermediate C, a 1:1 mixture of **4c** and **4d** (9.79 g, 28.0 mmol) were separated by SFC (column: DAICEL CHIRALPAK AD (250 × 30 mm, 10 μ m); mobile phase: [0.1% $\text{NH}_4\text{H}_2\text{O}$ MeOH]; B%: 0%-60%; 40 min) to give Intermediate D, 4-benzyloxy-7-bromo-1-chloro-phthalazine (2.40 g, 6.86 mmol) as a white solid and Intermediate E, 4-benzyloxy-6-bromo-1-chloro-phthalazine (2.54 g, 7.27) as a white solid. Intermediate D: 4-benzyloxy-7-bromo-1-chloro-phthalazine: ^1H NMR (400 MHz, CDCl_3) $\delta = 8.36$ (d, $J = 2.0$ Hz, 1H), 8.13 (d, $J = 8.8$ Hz, 1H), 7.99 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.58 - 7.54 (m, 2H), 7.46 - 7.36 (m, 3H), 5.70 (s, 2H). LCMS $[\text{M}+1]^+ 351.0$. Intermediate E: 4-benzyloxy-6-bromo-1-chloro-phthalazine: ^1H NMR (400 MHz, CDCl_3) $\delta = 8.39$ (d, $J = 1.6$ Hz, 1H), 8.10 - 8.01 (m, 2H), 7.61 - 7.54 (m, 2H), 7.48 - 7.35 (m, 3H), 5.70 (s, 2H). LCMS $[\text{M}+1]^+ 351.0$.

INTERMEDIATE F – Route 1



[0181] **Step 1:** To a solution of 1-(5-bromo-2-methyl-phenyl)ethenone **8c** (100 g, 445 mmol, 1.00 *eq.*) in water (1.00 L) was added potassium carbonate (92.4 g, 668 mmol, 1.50 *eq.*) and potassium permanganate (493 g, 3.12 mol, 7.00 *eq.*). The mixture was stirred at 50 °C for 3 hours before ethanol (1.00 L) was added and the resulting mixture stirred at 50 °C

for a further 30 minutes. After such time the solid was filtered and the filtrate pH adjusted to pH 2 with conc. hydrochloric acid (500 mL). The mixture was then extracted with ethyl acetate (1.00 L), the organic layer separated then concentrated in vacuo to give 4-bromo-2-oxalo-benzoic acid **9c** (278 g, 997 mmol, 75% yield) as a white solid which was used in the next step without further purification. LCMS $[M+1]^+ = 271.1$.

[0182] **Step 2:** To a solution of 4-bromo-2-oxalo-benzoic acid **9c** (382 g, 1.27 mol) in ethyl alcohol (3.00 L) was added hydrazine hydrate (71.2 g, 1.39 mol, 69.1 mL). The mixture was stirred at 75 °C for 4 hours and the formed precipitate was filtered, washed with ethyl alcohol (500 mL) and dried to give 7-bromo-4-oxo-3H-phthalazine-1-carboxylic acid **10c** (280 g, 1.03 mol, 81% yield) as a white solid which was used in the next step without further purification. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.72-8.81 (m, 1H), 8.11-8.21 (m, 1H), 7.95-8.09 (m, 1H).

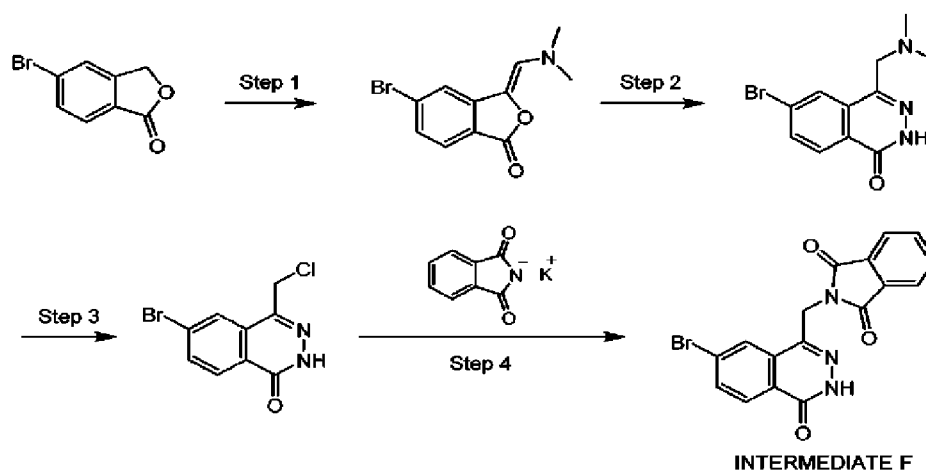
[0183] **Step 3:** To a solution of 7-bromo-4-oxo-3H-phthalazine-1-carboxylic acid **10c** (200 g, 675 mmol) in methyl alcohol (2.00 L) was added sulfuric acid (131 g, 1.31 mol, 71.0 mL) and the reaction mixture stirred at 65 °C for 24 hours. After such time the cooled reaction mixture was filtered and the filter cake dried under reduced pressure to give methyl 7-bromo-4-oxo-3H-phthalazine-1-carboxylate **11b** (216 g, crude) as a white solid which was used in the next step without further purification. LCMS $[M+1]^+ = 283.0$; ^1H NMR (400 MHz, DMSO- d_6) δ = 13.31 (s, 1H), 8.72 (s, 1H), 8.16-8.18 (d, $J = 8.4$ Hz, 1H), 8.03-8.05 (d, $J = 8.4$ Hz, 1H), 3.91 (s, 3H).

[0184] **Step 4:** A stirred solution of methyl 7-bromo-4-oxo-3H-phthalazine-1-carboxylate **11c** (159 g, 494 mmol) in ethyl alcohol (1.50 L) was treated portion wise with sodium borohydride (48.6 g, 1.29 mol, 2.60 eq) at 0 °C. To this mixture was added a solution of calcium chloride (65.8 g, 593 mmol, 1.20 eq). The mixture was then stirred for 2 hours at 0 °C and a further 1 hour at 20 °C. After such time the reaction mixture was concentrated under reduced pressure, and the residue was suspended in water (800 mL), the pH was adjusted to pH 5 with 1N hydrochloric acid (300 mL) and the precipitate was filtered, washed with water (300 mL $\times$ 3) and dried to give 6-bromo-4-(hydroxymethyl)-2H-phthalazin-1-one **12c** (162 g, crude) as a yellow solid. LCMS $[M+1]^+ = 255.0$; ^1H NMR (400 MHz, DMSO- d_6) δ = 12.66 (s, 1H), 8.30 (d, $J = 1.6$ Hz, 1H), 8.16 (d, $J = 8.8$ Hz, 1H), 8.01 (dd, $J = 8.4, 2.0$ Hz, 1H), 5.58 (t, $J = 5.6$ Hz, 1H), 4.67 (d, $J = 6.0$ Hz, 2H).

[0185] **Step 5:** 6-bromo-4-(hydroxymethyl)-2H-phthalazin-1-one **12c** (162 g, crude) was dissolved in thionyl chloride (1.00 L) and the mixture was stirred at 70 °C for 2 hours then concentrated under reduced pressure (35 °C). The concentrated residue was dissolved in dichloromethane (1.00 L) and concentrated to dryness to give 6-bromo-4-(chloromethyl)-2H-phthalazin-1-one **13c** (154 g, crude) as a white solid which was used in the next step without further purification. LCMS $[M+1]^+ = 274.8$; $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) $\delta = 12.92$ (s, 1H), 8.30 (s, 1H), 8.18-8.20 (d, $J = 7.6$ Hz, 1H), 8.06-8.08 (t, $J = 8.8$ Hz, 1H), 5.07 (s, 2H).

[0186] **Step 6:** To a solution of 6-bromo-4-(chloromethyl)-2H-phthalazin-1-one **13c** (148 g, crude) in DMF (1.5 L) was added (1,3-dioxoisindolin-2-yl)potassium (121 g, 653 mmol). The reaction mixture was stirred at 90 °C for 2 hours and then cooled to 25 °C. The formed precipitate was filtered and washed with DMF (200 mL x 2) and the filter cake triturated with water (1.00 L), filtered and dried to give Intermediate F, 2-[(7-bromo-4-oxo-3H-phthalazin-1-yl)methyl]isindoline-1,3-dione (162 g, 413 mmol, 76% yield) as a white solid. $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) $\delta = 12.59$ (s, 1H), 8.43 (d, $J = 1.2$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 8.07 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.97 - 7.93 (m, 2H), 7.92 - 7.86 (m, 2H), 5.19 (s, 2H). LCMS $[M+1]$: 383.9.

INTERMEDIATE F – Route 2



[0187] **Step 1:** A mixture of 5-bromoisobenzofuran-1(3H)-one (50.0 g, 235 mmol, 1.00 eq), DMF-DMA (180 g, 1.51 mol, 201 mL, 6.44 eq) and *t*-BuOK (2.63 g, 23.5 mmol, 0.10 eq) was degassed and purged with N_2 3 times and then stirred at 110 °C for 20 h under a N_2 atmosphere. After such time the reaction mixture concentrated under reduced pressure to remove the DMF-DMA and the formed residue was stirred in petroleum ether (100 mL) at 25

°C for 30 mins. The formed solid was filtered and the filter cake stirred in ethyl acetate (200 mL) at 80 °C for 12 h, filtered and the filter cake was dried under reduced pressure to give (Z)-5-bromo-3-((dimethylamino)methylene)isobenzofuran-1(3H)-one (39.0 g, 120 mmol, 51% yield, 82% purity) as a red solid. LCMS $[M+1]^+ = 270.1$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 7.97$ (d, $J = 1.2$ Hz, 1H), 7.61-7.59 (d, $J = 8.0$, 1H), 7.30-7.27 (dd, $J = 8.0$ & 1.2 Hz, 1H), 3.10 (s, 6H).

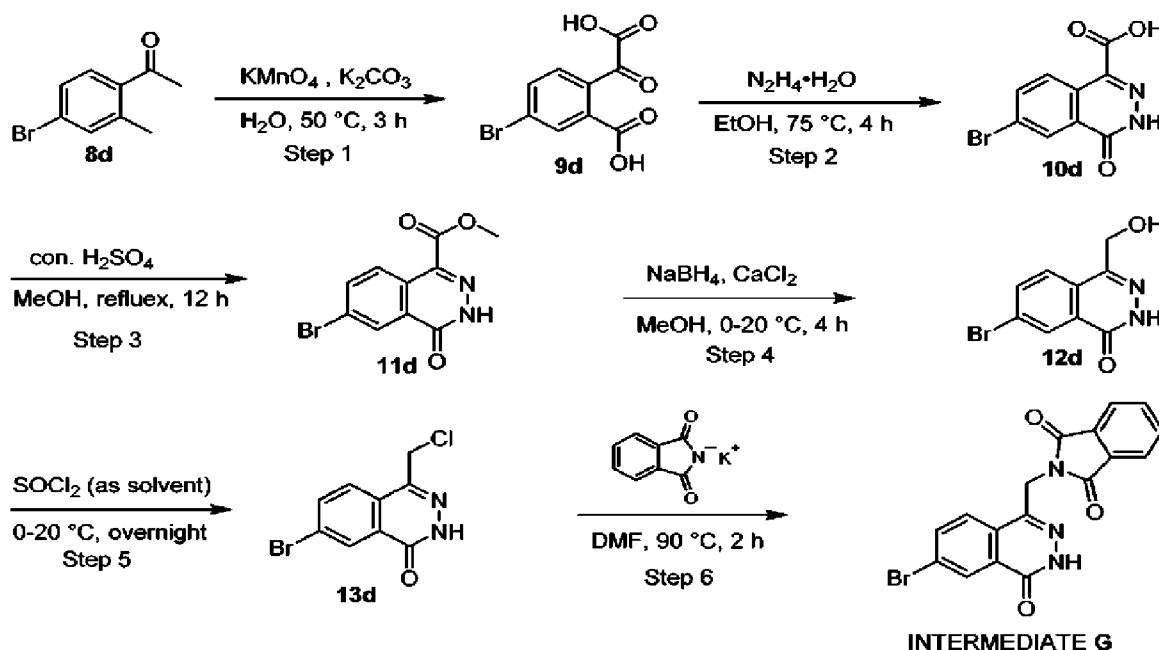
[0188] **Step 2:** To a mixture of (Z)-5-bromo-3-((dimethylamino)methylene)isobenzofuran-1(3H)-one (39.0 g, 119 mmol, 82.0% purity, 1.00 eq) in EtOH (650 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (12.5 g, 245 mmol, 12.1 mL, 2.05 eq) at 25 °C. The mixture was degassed with N_2 then stirred at 25 °C for 0.5 h and then at 70 °C for 12 h. After such time the reaction mixture was filtered and the solid was dried to give 6-bromo-4-((dimethylamino)methyl)phthalazin-1(2H)-one (30.0 g, 105 mmol, 88% yield, 99% purity) as a yellow solid. LCMS $[M+1]^+ = 282.1$; ^1H NMR (400 MHz, DMSO- d_6) δ 12.6 (s, 1H), 8.33 (s, 1H), 8.14-8.12 (d, $J=8.4$ Hz, 1H), 8.00-7.98 (m, 1H), 3.61 (s, 1H), 2.18 (s, 1H).

[0189] **Step 3:** A mixture of 6-bromo-4-((dimethylamino)methyl)phthalazin-1(2H)-one (15.0 g, 53.2 mmol, 1.00 eq) in THF (187 mL) and degassed with N_2 3 times before being cooled to 0 °C. Isobutyl carbonochloridate (8.71 g, 63.80 mmol, 8.38 mL, 1.20 eq) was then added dropwise and then the mixture stirred at 25 °C for 6 h under N_2 . After such time the mixture was cooled to 0 °C before HCl (0.5 M, 250 mL) was added maintaining a temperature between 0 °C and 10 °C. After the addition was complete the solid was filtered, washed with THF (30 mL x 3) and dried to afford a 6-bromo-4-(chloromethyl)phthalazin-1(2H)-one (11.0 g, 37.56 mmol, 71% yield, 93% purity) as a yellow solid. LCMS $[M+1]^+ = 256.1$; ^1H NMR (400 MHz, DMSO- d_6) δ 12.9 (s, 1H), 8.29 (d, $J = 1.6$ Hz, 1H), 8.19 - 8.17 (d, $J = 8.0$ Hz, 1H), 8.06 - 8.04 (dd, $J = 8.0$ Hz & 1.6 Hz, 1H), 5.06 (s, 2H).

[0190] **Step 4:** To a mixture of 6-bromo-4-(chloromethyl)phthalazin-1(2H)-one (8.06 g, 27.5 mmol, 93% purity, 1.00 eq) in DMF (160 mL) was added (1,3-dioxoisindolin-2-yl)potassium (5.61 g, 30.3 mmol, 1.10 eq) and stirred at 25 °C for 1 hr. After such time the mixture was washed with HCl (0.5 M, 100 mL), filtered and the solid washed with sat. NaHCO_3 . (30 mL x 2), pure water (30 mL x 2) and then triturated with EtOH (15 mL) at 70 °C for 1 hr. The solid was then filtered and dried to give Intermediate F (8.30 g, 17.9 mmol, 65.0% yield, 83% purity) as a yellow solid. LCMS $[M+1]^+ = 384.1/386.1$; ^1H NMR (400

MHz, DMSO-*d*₆) δ 12.6 (s, 1H), 8.43 (s, 1H), 8.18 - 8.16 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.95 - 7.89 (m, 4H), 5.18 (s, 2H).

INTERMEDIATE G



[0191] **Step 1:** To a solution of 1-(4-bromo-2-methylphenyl)ethenone **8d** (10.0 g, 46.9 mmol, 1.00 eq.) in water (50 mL) was added potassium carbonate (9.73 g, 70.40 mmol, 1.50 eq.) and potassium permanganate (51.9 g, 329 mmol, 7.00 eq.). The mixture was stirred at 50°C for 3 hours before ethanol (50 mL) was added and the resulting mixture stirred at 50°C for a further 30 minutes. After such time the solid was filtered and the filtrate pH adjusted to pH 2 with conc. hydrochloric acid (5 mL). The mixture was then extracted with ethyl acetate (50 mL), the organic layer separated and concentrated in vacuo to give 5-bromo-2-oxalo-benzoic acid **9d** (10.0 g, crude) as a white solid which was used in the next step without further purification. LCMS $[\text{M}+1]^+ = 273.0$.

[0192] **Step 2:** To a solution of 5-bromo-2-oxalo-benzoic acid **9d** (10.0 g, crude) in ethyl alcohol (120 mL) was added hydrazine hydrate (1.87 g, 36.6 mmol, 1.82 mL) and the mixture was stirred at 75°C for 4 hours. After such time the formed precipitate was filtered and washed with ethyl alcohol (5 mL) and dried to give 6-bromo-4-oxo-3H-phthalazine-1-carboxylic acid **10d** (7.50 g, 27.9 mmol, 59% yield) as a white solid. LCMS $[\text{M}+1]^+ = 269.0$.

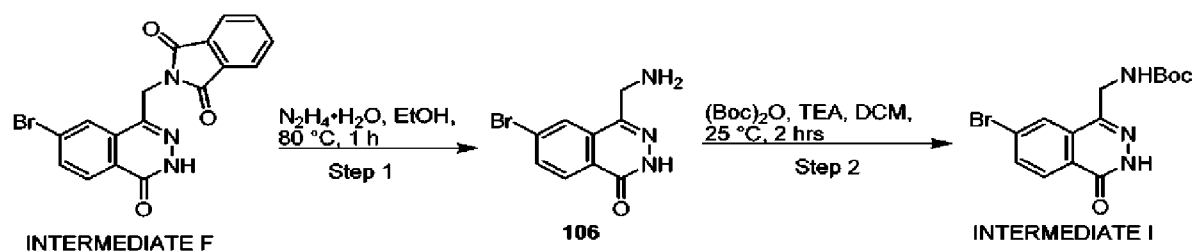
[0193] **Step 3:** To a solution of 6-bromo-4-oxo-3H-phthalazine-1-carboxylic acid **10d** (7.50 g, 27.9 mmol, 1.00 eq.) in methyl alcohol (40 mL) was added sulfuric acid (16.7 g, 167 mmol, 9.10 mL, 6.00 eq.) and the reaction mixture stirred at 65 °C for 12 hours. After such time the reaction mixture was allowed to cool and the formed precipitate was filtered and dried to give methyl 6-bromo-4-oxo-3H-phthalazine-1-carboxylate **11d** (7.00 g, 24.7 mmol, 89% yield) as a white solid. LCMS $[M+1]^+ = 282.9$.

[0194] **Step 4:** A stirred solution of sodium borohydride (2.43 g, 64.29 mmol, 2.60 eq.) in ethyl alcohol (250 mL) was treated portion wise with methyl 6-bromo-4-oxo-3H-phthalazine-1-carboxylate **11d** (7.00 g, 24.7 mmol, 1.00 eq.) at 0 °C. To this mixture was added a solution of calcium chloride (3.29 g, 29.7 mmol, 1.20 eq.) in ethyl alcohol (250 mL) in a dropwise fashion. The mixture was then stirred for 3 hours at 0 °C and an additional hour at 20 °C. After such time the mixture was concentrated under reduced pressure and the concentrated residue was suspended in water (30 mL) and the pH adjusted to pH 5 with 1N hydrochloric acid (5 mL). The formed precipitate was filtered, washed with water (5 mL $\times$ 3) and triturated with ethyl alcohol (50 mL), filtered and dried to give 7-bromo-4-(hydroxymethyl)-2H-phthalazin-1-one **12d** (6.00 g, 23.5 mmol, 95% yield) as a white solid. LCMS $[M+1]^+ = 255.0$.

[0195] **Step 5:** 7-bromo-4-(hydroxymethyl)-2H-phthalazin-1-one **12d** (6.00 g, 23.5 mmol) was dissolved in thionyl chloride (50 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours and then concentrated under reduced pressure (35 °C). The concentrated residue was dissolved in dichloromethane (20 mL) and concentrated to give 7-bromo-4-(chloromethyl)-2H-phthalazin-1-one **13d** (5.50 g, crude) as a white solid which was used in the next step without further purification. LCMS $[M+1]^+ = 275.0$.

[0196] **Step 6:** To a solution of 7-bromo-4-(chloromethyl)-2H-phthalazin-1-one **13d** (5.50 g, crude) in DMF (60.0 mL) was added (1,3-dioxoisindolin-2-yl)potassium (5.59 g, 30.2 mmol). The reaction mixture was stirred at 90 °C for 2 hours, then cooled to 25 °C and the formed precipitate was filtered and triturated with ethyl alcohol (150 mL) to give Intermediate G, 2-[(6-bromo-4-oxo-3H-phthalazin-1-yl)methyl]isoindoline-1,3-dione (5.00 g, 13.0 mmol, 65% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.66$ (s, 1H), 8.36 (d, $J = 2.0$ Hz, 1H), 8.22 - 8.18 (m, 1H), 8.14 - 8.10 (m, 1H), 7.97 - 7.93 (m, 2H), 7.91 - 7.87 (m, 2H), 5.18 (s, 2H). LCMS $[M+1]^+$: 386.1.

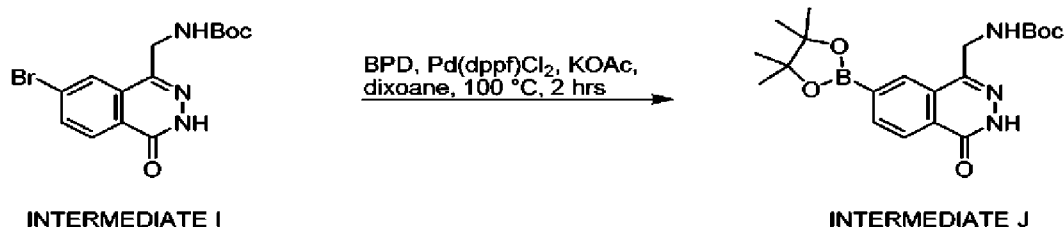
INTERMEDIATE I



[0197] **Step 1:** A solution of Intermediate F (3.00 g, 7.81 mmol, 1.00 eq.) and hydrazine hydrate (1.60 g, 31.2 mmol, 1.55 mL, 4.00 eq.) was stirred at 80 °C for 2 hours, cooled and concentrated under reduced pressure. The concentrated residue was then washed with water and triturated with ethyl alcohol at 25 °C to give 4-(aminomethyl)-6-bromo-2H-phthalazin-1-one **106** (1.95 g, 7.67 mmol, 98% yield) as a white solid. LCMS $[\text{M}+1]^+ = 256.1$.

[0198] **Step 2** To a solution of 4-(aminomethyl)-6-bromo-2H-phthalazin-1-one **106** (1.90 g, 7.48 mmol, 1.00 eq.) and triethylamine (2.27 g, 22.4 mmol, 3.12 mL, 3.00 eq.) in dichloromethane (40.0 mL) was added di-tert-butyl dicarbonate (3.26 g, 15.0 mmol, 3.44 mL, 2.00 eq.). The mixture was stirred at 25 °C for 2 hours, filtered and concentrated under reduced pressure to give a residue. The concentrated residue was triturated with dichloromethane (40 mL) then filtered and dried to give t-butyl-N-[(7-bromo-4-oxo-3H-phthalazin-1-yl)methyl]carbamate, Intermediate I (1.97 g, 5.56 mmol, 74% yield) as a white solid. LCMS $[\text{M}+1]^+ = 356.1$. ^1H NMR (400 MHz, DMSO- d_6) δ = 12.71 (s, 1H), 8.26 (br s, 1H), 8.16 (br d, J = 8.0 Hz, 1H), 8.02 (br d, J = 8.0 Hz, 1H), 7.46 (br s, 1H), 4.41 (br d, J = 4.4 Hz, 2H), 1.40 (br s, 9H).

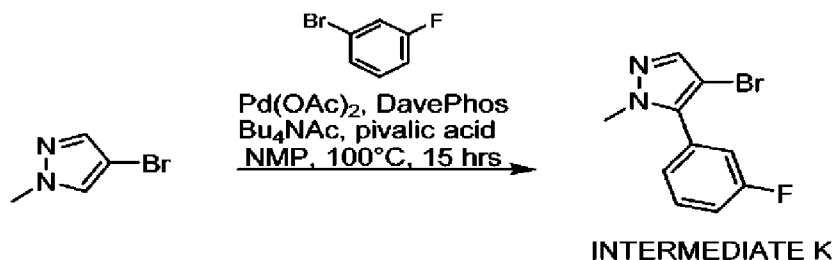
INTERMEDIATE J



[0199] A mixture of Intermediate I (130.0, 275 mmol, 1.00 eq.), bis(pinacolato)diboron (BPD) (104.9 g, 412.9 mmol, 1.50 eq.), Pd(dppf)Cl₂ (20.1 g, 27.5 mmol, 0.10 eq.), KOAc (81.0 g, 825 mmol, 3.00 eq.) in dioxane (2.60 L) was degassed and purged with N₂. The

mixture was then stirred at 100 °C for 2 hours. After such time the mixture was filtered, concentrated and the residue triturated with petroleum ether/ethyl acetate 10/1 (400 mL) at 25 °C for 1 hr. The solid was then filtered and dried to give Intermediate J as a brown solid (68.0 g, 162 mmol, 59% yield). LCMS $[M+1]^+ = 402.3$; ^1H NMR (400 MHz, CDCl_3) $\delta = 12.62$ (s, 1H), 8.25 (s, 2H), 8.01-8.13 (m, 1H), 7.21-7.45 (m, 1H), 4.34-4.63 (m, 2H), 1.42 (s, 9H), 1.32 (s, 12H).

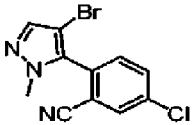
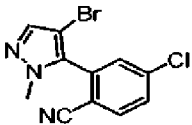
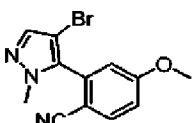
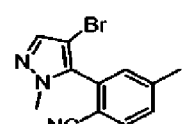
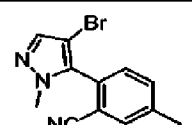
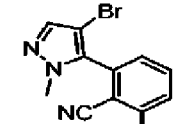
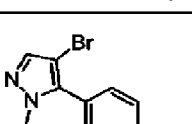
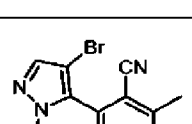
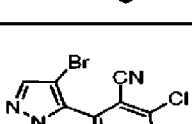
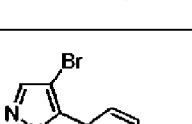
INTERMEDIATE K

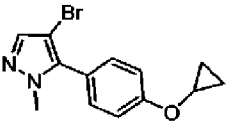
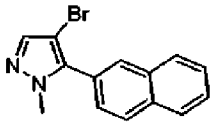
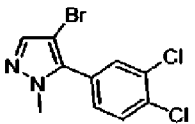
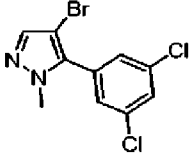
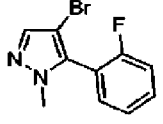
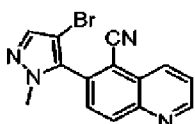
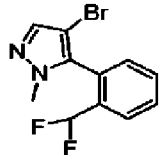
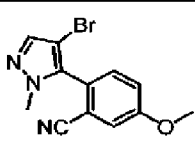
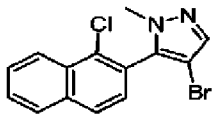


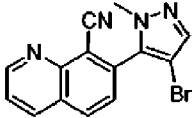
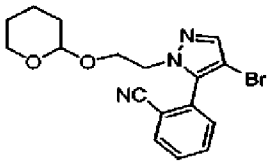
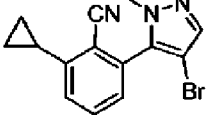
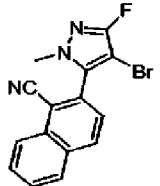
[0200] A solution of 4-bromo-1-methyl-pyrazole (500 mg, 3.11 mmol, 1.00 *eq.*) and the 1-bromo-3-fluoro-benzene (543 mg, 3.11 mmol, 346 μL , 1.00 *eq.*) in N-methylpyrrolidone (10 mL) was degassed with nitrogen. Then, palladium acetate (7.0 mg, 31.1 μmol , 0.10 *eq.*) and 2-(2-dicyclohexylphosphanylphenyl)-*N,N*-dimethyl-aniline (DavePhos) (24.0 mg, 62.1 μmol , 0.02 *eq.*) was added. To the resulting dark brown solution, tetrabutylammonium acetate (1.87 g, 6.21 mmol, 2 mL, 2.00 *eq.*) and pivalic acid (317 mg, 3.11 mmol, 357 μL , 1.00 *eq.*) were added and the resulting solution stirred at 100°C for 15 hours. After the reaction was completed, the mixture was cooled. Ethyl acetate (100 mL) was added and the resulting mixture was washed with brine (3×100 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo to give a crude oil. The crude oil was purified by silica gel chromatography (petroleum ether/ ethyl acetate 0-10%) to give 4-bromo-5-(3-fluorophenyl)-1-methyl-1*H*-pyrazole, Intermediate K (600 mg, 2.35 mmol, 76% yield) as a colorless oil. LCMS $[M+1]^+ = 255.0$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.56$ (s, 1H), 7.50 (dt, $J = 6.0, 8.0$ Hz, 1H), 7.24 - 7.18 (m, 2H), 7.18 - 7.13 (m, 1H), 3.85 (s, 3H).

[0201] The Intermediates A-1 to A-32 shown in Table I-I were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE K.

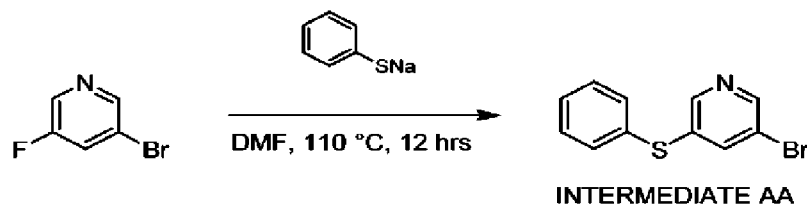
Table I-I		
Intermediate	Structure	Spectral Data
A-1		4-bromo-5-(3-chlorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 353.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.47 - 7.43 (m, 2H), 7.42 - 7.40 (m, 1H), 7.30 (dt, J = 1.6, 4.4 Hz, 1H), 3.83 (s, 3H)
A-2		4-bromo-5-(3-methoxyphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 267.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.93 (s, 1H), 7.51 (s, 1H), 7.50 - 7.44 (t, J=8.4, 1H), 7.11 - 7.07 (m, 1H), 7.05 - 7.03 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H)
A-3		4-bromo-5-(3-methylphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 251.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.50 (s, 1H), 7.39 - 7.33 (m, 1H), 7.25 (br d, J = 7.6 Hz, 1H), 7.21 - 7.14 (m, 2H), 3.79 (s, 3H), 2.41 (s, 3H)
A-4		4-bromo-5-(4-fluorophenyl)-1-methyl-1H-pyrazole ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.65 (s, 1H), 7.58 - 7.54 (m, 2H), 7.42 - 7.38 (m, 2H), 3.35 (s, 3H)
A-5		4-bromo-5-(4-chlorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 272.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 3.82 (s, 3H) 7.34 - 7.38 (d, J = 8.8 Hz, 2H) 7.48 - 7.52 (d, J = 8.8 Hz, 2H) 7.55 (s, 1H)
A-6		4-bromo-5-(4-methylphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 251.0
A-7		4-bromo-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 269.0; ¹ H NMR (400 MHz, CDCl ₃ - <i>d</i>) δ = 7.53 (s, 1H), 7.36 - 7.32 (m, 2H), 7.05 - 7.01 (m, 2H), 3.88 (s, 3H), 3.81 (s, 3H)
A-8		5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-methylpyridine LCMS [M+1] ⁺ = 252.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.56 (d, J = 2.4 Hz, 1H), 7.65 (dd, J = 2.4, 8.0 Hz, 1H), 7.56 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 2.65 (s, 3H)
A-9		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-benzonitrile ¹ H NMR (400 MHz, CDCl ₃) δ = 7.86 (dd, J = 0.8, 7.6 Hz, 1H), 7.76 (dt, J = 1.2, 7.6 Hz, 1H), 7.63 (dt, J = 1.2, 7.6 Hz, 1H), 7.60 (s, 1H), 7.49 (dd, J = 0.8, 7.6 Hz, 1H), 3.81 (s, 3H)

A-10		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chlorobenzonitrile LCMS [M+1] ⁺ = 297.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.84 (d, J = 2.0 Hz, 1 H) 7.73 (dd, J = 8.4, 2.0 Hz, 1 H) 7.60 (s, 1 H) 7.43 (d, J = 8.4 Hz, 1 H) 3.81 (s, 3 H)
A-11		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chlorobenzonitrile ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.13 (d, J = 8.4 Hz, 1H), 7.93 - 7.90 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 2.0, 8.4 Hz, 1H), 7.76 (s, 1H), 3.75 (s, 3H)
A-12		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methoxybenzonitrile LCMS [M+1] ⁺ = 294.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.77 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.09 (dd, J = 2.8, 8.8 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H)
A-13		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methylbenzonitrile LCMS [M+1] ⁺ = 276.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.73 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.42 (dd, J = 0.8, 8.0 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H), 2.51 (s, 3H)
A-14		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methylbenzonitrile LCMS [M+1] ⁺ = 276.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.50 (s, 1H), 7.48 (br d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 3.72 (s, 3H), 2.42 (s, 3H)
A-15		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-methoxybenzonitrile LCMS [M+1] ⁺ = 292.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.87 - 7.80 (m, 1H), 7.74 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 3.99 (s, 3H), 3.71 (s, 3H)
A-16		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methoxybenzonitrile LCMS [M+1] ⁺ = 294.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.50 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 2.8 Hz, 1H), 7.21 - 7.17 (m, 1H), 3.84 (s, 3H), 3.71 (s, 3H)
A-17		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-methylbenzonitrile LCMS [M+1] ⁺ = 278.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.80 (t, J = 7.6 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 3.70 (s, 3H), 2.58 (s, 3H)
A-18		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-chlorobenzonitrile LCMS [M+1] ⁺ = 298.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.98 (dd, J = 1.2, 6.8 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.77 (s, 1H), 7.69 (dd, J = 1.2 Hz, 1H), 3.75 (s, 3H)
A-19		4-bromo-5-(4-ethylphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 265.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.33 (m, 4H), 3.82 (s, 3H), 2.81 - 2.71 (m, 2H), 1.31 (t, J = 7.6 Hz, 3H)

A-20		4-bromo-5-(4-cyclopropoxyphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 295.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.36 - 7.33 (m, 2H), 7.21-7.18 (m, 2H), 3.84 (s, 3H), 3.83 - 3.78 (m, 1H), 0.87 - 0.84 (m, 2H), 0.83 (m, 2H)
A-21		4-bromo-1-methyl-5-(naphthalen-2-yl)-1H-pyrazole LCMS [M+1] ⁺ = 289.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.98 (d, J = 8.4 Hz, 1H), 7.95 - 7.87 (m, 3H), 7.63 - 7.55 (m, 3H), 7.50 (dd, J = 1.6, 8.4 Hz, 1H), 3.88 (s, 3H)
A-22		4-bromo-5-(3,4-dichlorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 306.8; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.60 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.27 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 3.83 (s, 3H)
A-23		4-bromo-5-(3,5-dichlorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 306.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.55 (s, 1H), 7.48 (t, J = 1.8 Hz, 1H), 7.31 (d, J = 2.0 Hz, 2H), 3.84 (s, 3H)
A-24		4-bromo-5-(2-fluorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 255.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.57 (s, 1H), 7.54 - 7.47 (m, 1H), 7.41 - 7.37 (m, 1H), 7.30 (br t, J = 8.0 Hz, 1H), 7.26 - 7.20 (m, 1H), 3.79 (s, 3H)
A-25		6-(4-bromo-1-methyl-1H-pyrazol-5-yl)quinoline-5-carbonitrile LCMS [M+1] ⁺ = 313.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 9.15 (dd, J = 1.6, 4.0 Hz, 1H), 8.67 (dd, J = 0.8, 8.4 Hz, 1H), 8.49 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 4.0, 8.4 Hz, 1H), 7.67 (s, 1H), 3.88 (s, 3H)
A-26		4-bromo-5-(2-(difluoromethyl)phenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 287.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.86 - 7.80 (m, 1H), 7.69 - 7.60 (m, 2H), 7.58 (s, 1H), 7.32 - 7.28 (m, 1H), 6.59 - 6.27 (m, 1H), 3.65 (s, 3H)
A-27		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methoxybenzonitrile LCMS [M+1] ⁺ = 294.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.50 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 2.8 Hz, 1H), 7.21 - 7.17 (m, 1H), 3.84 (s, 3H), 3.71 (s, 3H)
A-28		4-bromo-5-(1-chloronaphthalen-2-yl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 323.2; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.41 (d, J = 8.4 Hz, 1H), 8.00 - 7.87 (m, 2H), 7.77 - 7.62 (m, 3H), 7.37 (d, J = 8.4 Hz, 1H), 3.77 (s, 3H)

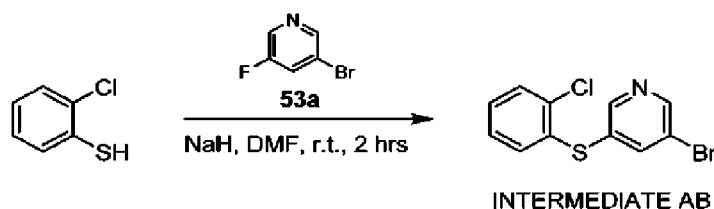
A-29		7-(4-bromo-1-methyl-1H-pyrazol-5-yl)quinoline-8-carbonitrile LCMS $[M+1]^+ = 313.2$; ^1H NMR (400 MHz, CDCl_3) $\delta = 9.19$ (dd, $J = 1.6, 4.0$ Hz, 1H), 8.34 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.72 - 7.60 (m, 3H), 3.89 (s, 3H)
A-30		2-(4-bromo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-pyrazol-5-yl)benzonitrile LCMS $[M-83]^+ = 292.1$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.84$ (d, $J = 7.9$ Hz, 1H), 7.76 - 7.70 (m, 1H), 7.65 (s, 1H), 7.63 - 7.58 (m, 1H), 7.58 - 7.51 (m, 1H), 4.49 - 4.40 (m, 1H), 4.31 - 4.03 (m, 3H), 4.01 - 3.81 (m, 1H), 3.76 - 3.62 (m, 1H), 3.48 - 3.36 (m, 1H), 1.60 - 1.38 (m, 6H)
A-31		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-cyclopropylbenzonitrile LCMS $[M+1]^+ = 397.3$; ^1H NMR (400 MHz, CD_3OD) $\delta = 8.23$ (d, $J = 8.4$ Hz, 1H), 8.14 (s, 1H), 7.81 - 7.75 (m, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.57 (s, 1H), 7.50 - 7.45 (m, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 3.85 (s, 2H), 3.80 (s, 3H), 2.36 - 2.19 (m, 1H), 1.24 - 1.17 (m, 2H), 0.98 - 0.86 (m, 2H)
A-32		2-(4-bromo-3-fluoro-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS $[M+1]^+ = 330.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.33$ (d, $J = 8.4$ Hz, 1H), 8.21 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 7.6$ Hz, 1H), 7.80 (dt, $J = 1.2, 7.6$ Hz, 1H), 7.76 - 7.70 (m, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 3.72 (s, 3H)

INTERMEDIATE AA



[00100] To a solution of 3-bromo-5-fluoropyridine (2.20 g, 12.5 mmol, 1.00 *eq.*) in dimethylformamide (50 mL) was added phenylsulfanylsodium (1.98 g, 15.0 mmol, 1.20 *eq.*) followed by stirring at 110 °C for 12 hours. After such time the reaction mixture was diluted with water (700 mL) and extracted with ethyl acetate (150 mL $\times$ 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 0-10%) to give 3-bromo-5-phenylsulfanylpyridine, Intermediate AA (1.31 g, 4.48 mmol, 35% yield) as a yellow oil. LCMS $[M+1]^+ = 268.0$; ^1H NMR (400 MHz, MeOD) $\delta = 8.44$ (d, $J = 2.0$ Hz, 1H), 8.31 (d, $J = 2.0$ Hz, 1H), 7.73 (t, $J = 2.0$ Hz, 1H), 7.50 - 7.46 (m, 2H), 7.45 - 7.41 (m, 3H).

INTERMEDIATE AB



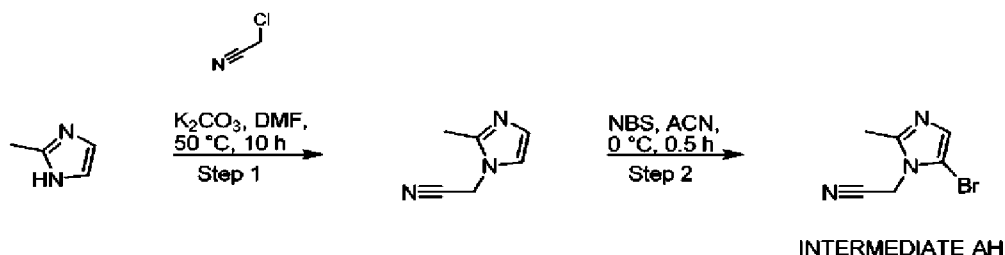
[0202] To a solution of 2-chlorobenzenethiol (296 mg, 2.05 mmol, 233 μ L, 1.20 *eq.*) in DMF (2 mL) was added sodium hydride (82 mg, 2.05 mmol, 60% purity, 1.20 *eq.*) and 3-bromo-5-fluoro-pyridine (300 mg, 1.70 mmol, 1.00 *eq.*) and stirred at 25 °C for 2 hours. The reaction mixture was then quenched by addition water (10 mL) and then extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate 20%) to give 3-bromo-5-(2-chlorophenyl)sulfanylpromidine, Intermediate AB (280 mg, 931 μ mol, 54% yield) as a white solid. LCMS $[M+1]^+ = 302.0$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ = 8.56 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.73 (t, J = 2.0 Hz, 1H), 7.51 - 7.47 (m, 1H), 7.33 - 7.28 (m, 2H), 7.26 - 7.22 (m, 1H).

[0203] The INTERMEDIATES AC to AG shown in Table I-IIa were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE AB.

Table I-IIa		
Intermediate	Structure	Characterization
AC		3-bromo-5-((4-chlorophenyl)thio)pyridine LCMS $[M+1]^+ = 302.0$
AD		3-bromo-5-((3-chlorophenyl)thio)pyridine LCMS $[M+1]^+ = 302.0$; ^1H NMR (400 MHz, CDCl_3) δ = 8.55 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 7.74 (t, J = 2.0 Hz, 1H), 7.40 - 7.38 (m, 1H), 7.34 - 7.30 (m, 2H), 7.29 - 7.27 (m, 1H)
AE		3-bromo-5-((o-tolyl)thio)pyridine LCMS $[M+1]^+ = 280.0$; ^1H NMR (400 MHz, CDCl_3) δ = 8.45 (br s, 1H), 8.29 (br s, 1H), 7.48 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37 - 7.31 (m, 2H), 7.26 - 7.21 (m, 1H), 2.40 (s, 3H)
AF		3-bromo-5-((p-tolyl)thio)pyridine LCMS $[M+1]^+ = 281.0$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.53 (d, J = 1.6 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.82 (q, J = 2.4 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.31 - 7.23 (m, 2H), 7.11 - 7.06 (m, 1H)

AG		3-bromo-5-(m-tolylthio)pyridine LCMS [M+1] ⁺ = 279.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.48 (d, <i>J</i> = 2.0 Hz, 1H), 8.40 (d, <i>J</i> = 1.6 Hz, 1H), 7.67 - 7.61 (m, 1H), 7.34 - 7.28 (m, 3H), 7.21 - 7.19 (m, 1H), 2.38 (s, 3H)

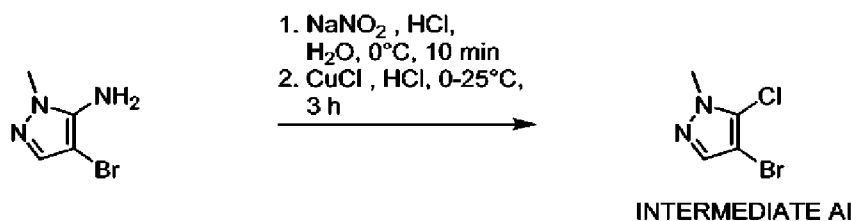
INTERMEDIATE AH



[0204] **Step 1:** To a solution of 2-methyl-1*H*-imidazole (1.00 g, 12.2 mmol, 1.00 *eq.*) in DMF (10 mL) was added potassium carbonate (1.68 g, 12.2 mmol, 1.00 *eq.*) and 2-chloroacetonitrile (920 mg, 12.2 mmol, 773 μ L, 1.00 *eq.*) and the mixture stirred at 50 °C for 5 hours. After such time the reaction mixture was diluted with water (20 mL), extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-100%) to give 2-(2-methylimidazol-1-yl)acetonitrile (460 mg, 3.80 mmol, 31% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 6.98 (d, *J* = 1.2 Hz, 1H), 6.94 (d, *J* = 1.2 Hz, 1H), 4.79 (s, 2H), 2.47 (s, 3H).

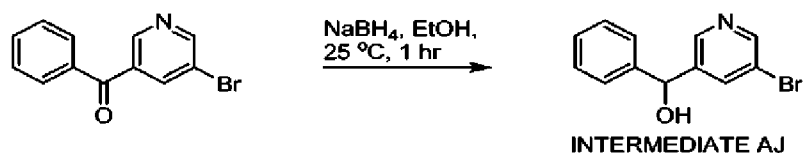
[0205] **Step 2:** To a solution of 2-(2-methylimidazol-1-yl)acetonitrile (410 mg, 3.38 mmol, 1.00 *eq.*) in acetonitrile (10 mL) was added a solution of *N*-bromosuccinimide (542 mg, 3.05 mmol, 0.90 *eq.*) in acetonitrile (10 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and after such time the reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 mL $\times$ 3). The combined organic phases were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a residue. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-100%) followed by a second column (SiO₂, petroleum ether: ethyl acetate: methanol 1: 1: 0.4) to give 2-(5-bromo-2-methylimidazol-1-yl)acetonitrile, Intermediate AH (460 mg, 2.30 mmol, 67% yield) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ = 6.97 (s, 1H), 4.82 (s, 2H), 2.53 (s, 3H).

INTERMEDIATE AI



[0206] To a solution of 4-bromo-2-methyl-pyrazol-3-amine (0.20 g, 1.14 mmol, 1.00 *eq.*) in hydrochloric acid (12 M, 2 mL, 21.1 *eq.*) was slowly added a solution of sodium nitrite (86 mg, 1.25 mmol, 1.10 *eq.*) in water (1.8 mL) at 0°C . After stirring for 10 minutes, the mixture was added in portions to a solution of cuprous chloride (112 mg, 1.14 mmol, 27.2 μL , 1.00 *eq.*) in hydrochloric acid (12 M, 1.00 mL, 10.6 *eq.*). The reaction mixture was stirred at 25°C for 3 hours. After such time the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL $\times$ 3). Combined organic phases were washed with aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (petroleum ether:ethyl acetate 25%) to give 4-bromo-5-chloro-1-methyl-pyrazole, Intermediate AI (92 mg, 363 μmol , 31% yield) as a white solid. LCMS $[\text{M}+1]^+ = 197.0$; ^1H NMR (400 MHz, CDCl_3 -*d*) $\delta = 7.48$ (s, 1H), 3.88 (s, 3H).

INTERMEDIATE AJ



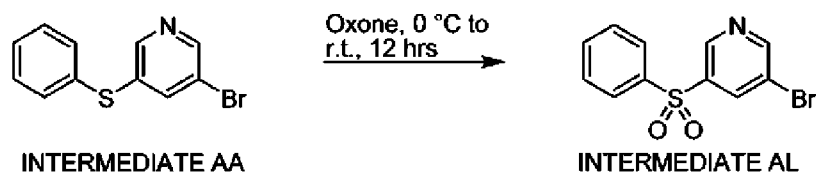
[0207] Sodium borohydride (22 mg, 572 μmol , 1.50 *eq.*) was added slowly to a solution of (5-bromo-3-pyridyl)-phenyl-methanone (100 mg, 381 μmol , 1.00 *eq.*) in ethyl alcohol (5 mL). After stirring at 25°C for 2 hours the reaction was quenched with water (2 mL) and concentrated under vacuum. The residue was diluted with ethyl acetate (10 mL), washed with brine (10 $\times$ 3 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (5-bromopyridin-3-yl)(phenyl)methanol, Intermediate AJ (97 mg, 367 μmol , 96% yield) as a colorless oil. LCMS $[\text{M}+1]^+ = 263.9$. ^1H NMR (400 MHz, CDCl_3) $\delta = 8.53$ (d, $J = 2.0$ Hz, 1H), 8.48 (d, $J = 2.0$ Hz, 1H), 7.89 (t, $J = 2.0$ Hz, 1H), 7.43 - 7.38 (m, 1H), 7.38 - 7.31 (m, 4H), 5.85 (s, 1H), 2.85 (s, 1H).

INTERMEDIATE AK



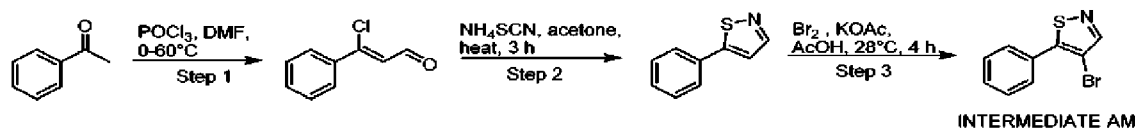
[0208] To a solution of 3-bromo-5-(phenylthio)pyridine, Intermediate AA (200 mg, 751 μmol , 1.00 *eq.*) in dichloromethane (4 mL) was added 3-chloroperoxybenzoic acid (153 mg, 751 μmol , 85.0% purity, 1.00 *eq.*). The resulting mixture was stirred at 25 °C under nitrogen for 1 hour. After such time sodium hydroxide aqueous solution (4 N, 40 mL) was added and the mixture extracted with dichloromethane (20 mL $\times$ 2). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over sodium sulfate and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5-20%) to give 3-bromo-5-(phenylsulfinyl)pyridine, Intermediate AK (150 mg, 532 μmol , 70% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.72 (d, *J* = 2.0 Hz, 1H), 8.66 (d, *J* = 2.0 Hz, 1H), 8.16 (t, *J* = 2.0 Hz, 1H), 7.72 - 7.68 (m, 2H), 7.55-7.27 (m, 3H).

INTERMEDIATE AL



[0209] A solution of oxone (2.10 g, 3.42 mmol, 2.00 *eq.*) in water (10 mL) was added to a solution of 3-bromo-5-phenylsulfanyl-pyridine intermediate AA (500 mg, 1.71 mmol, 1.00 *eq.*) in THF (10 mL) and methyl alcohol (10 mL) at 0 °C. The resulting mixture was stirred at 35 °C for 12 hours and after such time was filtered and the filtrate concentrated under reduced pressure. The formed residue was purified by reversed-phase HPLC (0.1% FA condition) to give 3-(benzenesulfonyl)-5-bromo-pyridine, Intermediate AL (300 mg, 1.01 mmol, 59% yield) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ = 9.13 (d, *J* = 2.0 Hz, 1H), 9.01 (d, *J* = 2.0 Hz, 1H), 8.66 (t, *J* = 2.0 Hz, 1H), 8.12 - 8.08 (m, 2H), 7.77 - 7.72 (m, 1H), 7.69 - 7.64 (m, 2H).

INTERMEDIATE AM



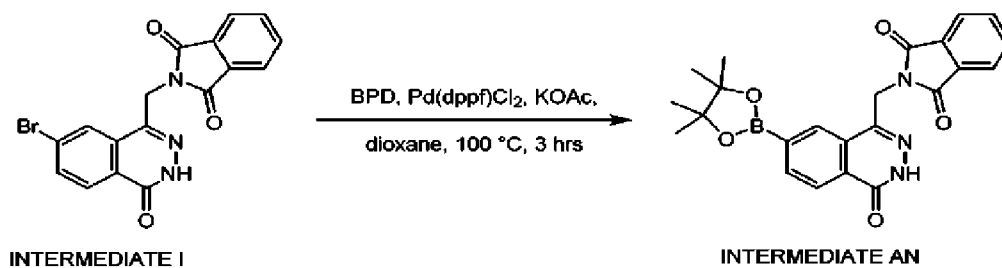
[0210] **Step 1:** Phosphorus oxychloride (4.71 g, 30.7 mmol, 2.9 mL, 1.23 *eq.*) was added dropwise to DMF (6 mL) at 0 °C, and then the mixture was stirred at 0 °C for 10 minutes. After such time a solution of 1-phenylethanone (3.00 g, 25.0 mmol, 2.91 mL, 1.00 *eq.*) in DMF (25 mL) was added dropwise with stirring. The reaction mixture was then heated 3 hours at 60 °C. After such time the solution was cooled to room temperature and poured slowly into an aqueous sodium acetate solution (10%, 100 mL). The pH was adjusted to 4 with additional sodium acetate solution (10 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (Z)-3-chloro-3-phenyl-prop-2-enal (2.50 g, 14.1 mmol, 56% yield) as a yellow oil. LCMS $[M+1]^+ = 167.1$. $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 10.24$ (d, $J = 6.8$ Hz, 1H), 7.49 (m, 5H), 6.69 (d, $J = 6.8$ Hz, 1H).

[0211] **Step 2:** Hydrogen Cyanide (HCN) is produced as a byproduct in this reaction. Appropriate safety precaution and procedures should be employed. A mixture of (Z)-3-chloro-3-phenyl-prop-2-enal (1.76 g, 10.6 mmol, 1.00 *eq.*), ammonium thiocyanate (1.61 g, 21.1 mmol, 1.61 mL, 2.00 *eq.*) in acetone (25 mL) was degassed and purged with nitrogen and stirred at 80 °C for 1 hour. After such time the cooled mixture was poured into saturated sodium bicarbonate aqueous solution (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The formed residue was purified by column chromatography (SiO_2 , petroleum ether/ ethyl acetate 0-50%) to give 5-phenylisothiazole (1.00 g, 6.20 mmol, 58% yield) as a yellow oil. LCMS $[M+1]^+ = 162.2$. $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 8.49$ (d, $J = 2.0$ Hz, 1H), 7.64 - 7.60 (m, 2H), 7.48 - 7.43 (m, 3H), 7.42 (d, $J = 2.0$ Hz, 1H).

[0212] **Step 3:** Bromine (952 mg, 5.95 mmol, 307 μL , 3.20 *eq.*) was added dropwise over a period of 30 min to a stirred mixture of 5-phenylisothiazole (300 mg, 1.86 mmol, 1.00 *eq.*), potassium acetate (365 mg, 3.72 mmol, 2.00 *eq.*) and acetic acid (12 mL). The reaction mixture was stirred at 25 °C 5 hours and after such time treated with aqueous sodium bisulfite (33%, 10 mL). The solution was made basic with aqueous sodium hydroxide (20%, 10 mL),

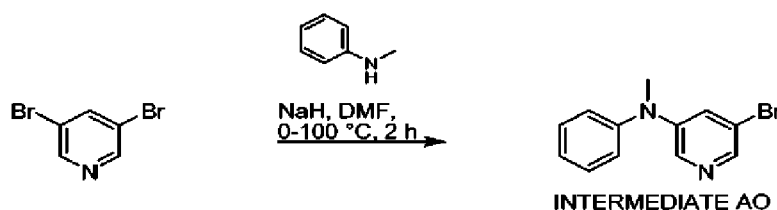
extracted with dichloromethane (3×80 mL). The combined organic extracts were dried (anhydrous sodium sulfate), filtered and concentrated to give to 4-bromo-5-phenyl-isothiazole, Intermediate AM (300 mg, 1.25 mmol, 67% yield) as colorless oil. LCMS $[M+1]^+ = 240.9$. ^1H NMR (400 MHz, CDCl_3) δ = 8.39 (s, 1H), 7.69 - 7.65 (m, 2H), 7.52 - 7.47 (m, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ = 161.0, 159.5, 129.9, 129.3, 129.0, 128.5, 106.0.

INTERMEDIATE AN



[0213] A mixture of intermediate I (160 g, 416 mmol, 1.00 eq.), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (BPD) (158 g, 624 mmol, 1.50 eq.), $\text{Pd}(\text{dppf})\text{Cl}_2$ (30.4 g, 41.6 mmol, 0.10 eq.), potassium acetate (122 g, 1.25 mol, 3.00 eq.) in dioxane (2.0 L) was purged with nitrogen and stirred at 100 °C for 3 hrs. After such time the reaction mixture was filtered and concentrated under reduced pressure. The residue was triturated with MeOH (1.0 L) at 25 °C for 2 h, filtered and dried to give 2-((4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione, Intermediate AN (93.0 g, 209 mmol, 50% yield) as a gray solid. LCMS $[M+1]^+ = 432.4$. ^1H NMR: (400 MHz $\text{DMSO}-d_6$) δ : 12.54 (s, 1H), 8.24-8.37 (m, 2H), 8.13 (d, $J = 7.6$ Hz, 1H), 7.93-7.99 (m, 2H), 7.87-7.93 (m, 2H), 5.22 (s, 2H), 1.36 (s, 12H).

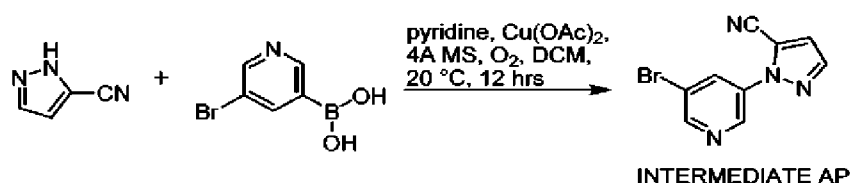
INTERMEDIATE AO



[0214] To a solution of 3,5-dibromopyridine (1.00 g, 4.22 mmol, 1.00 eq.) in DMF (10 mL) was added sodium hydride (270 mg, 6.75 mmol, 60% purity, 1.60 eq.) at 0 °C over 10 min followed by *N*-methylaniline (452 mg, 4.22 mmol, 458 μL , 1.00 eq.). The resulting mixture was stirred at 100 °C for 2 hours. After such time the reaction mixture was diluted with water

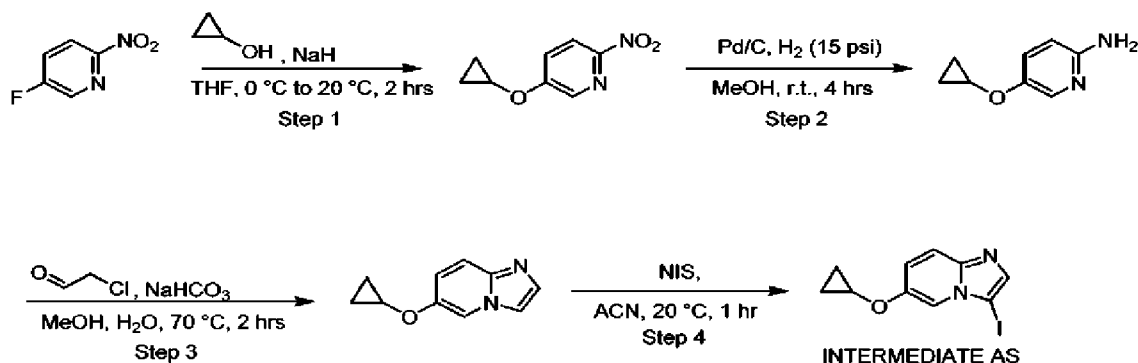
(10 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (400 g SiO₂, water/acetonitrile, 0-100% 70 mL/min) to give 5-bromo-*N*-methyl-*N*-phenyl-pyridin-3-amine, Intermediate AO (50.0 mg, 190 μ mol, 5% yield) as a yellow solid. LCMS $[M+1]^+$ 262.9. ¹H NMR (400 MHz, CDCl₃-*d*) δ = 8.12 (br d, *J* = 6.4 Hz, 2H), 7.44 - 7.35 (m, 2H), 7.26 - 7.24 (m, 1H), 7.23 - 7.19 (m, 1H), 7.19 - 7.17 (m, 1H), 7.17 - 7.14 (m, 1H), 3.33 (s, 3H).

INTERMEDIATE AP



[0215] A mixture of (5-bromo-3-pyridyl)boronic acid (325 mg, 1.61 mmol, 1.50 *eq.*), 1*H*-pyrazole-5-carbonitrile (100 mg, 1.07 mmol, 1.00 *eq.*), pyridine (255 mg, 3.22 mmol, 260 μ L, 3.00 *eq.*), 4Å molecular sieves (20.0 mg, 1.07 mmol) and copper acetate (585 mg, 3.22 mmol, 3.00 *eq.*) in dichloromethane (5 mL) was degassed with nitrogen and stirred at 20 °C for 12 hours under an oxygen atmosphere (15 psi). After such time the reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5-20%) to give 2-(5-bromo-3-pyridyl)pyrazole-3-carbonitrile, Intermediate AP (150 mg, 602 μ mol, 56% yield) as a white solid. LCMS $[M+1]^+$ 249.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.15 (d, *J* = 2.4 Hz, 1H), 8.91 (d, *J* = 2.4 Hz, 1H), 8.78 (d, *J* = 2.0 Hz, 1H), 8.63 (t, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 2.4 Hz, 1H).

INTERMEDIATE AS



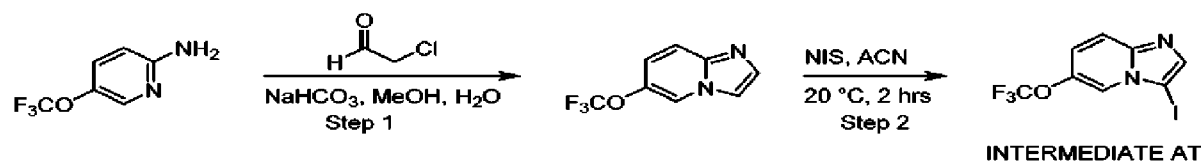
[0216] **Step 1:** To a solution of cyclopropanol (450 mg, 7.74 mmol, 1.10 *eq.*) in THF (10 mL) was added sodium hydride (310 mg, 7.74 mmol, 60.0% purity, 1.10 *eq.*) at 0 °C, followed by 5-fluoro-2-nitro-pyridine (1.00 g, 7.04 mmol, 1.00 *eq.*) and the mixture was warmed to 20 °C and stirred for 2 hours. After completion, the mixture was filtered and concentrated in vacuum and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 20-80%) to give 5-(cyclopropoxy)-2-nitro-pyridine (1.10 g, 6.11 mmol, 86% yield) as a white solid. LCMS [M+1]⁺ = 181.1.

[0217] **Step 2:** To a solution of 5-(cyclopropoxy)-2-nitro-pyridine (200 mg, 1.11 mmol, 1.00 *eq.*) in methyl alcohol (4 mL) was added palladium on activated carbon (100 mg, 1.11 mmol, 10% purity, 1.00 *eq.*) and the mixture was stirred at 30 °C for 4 hours under a hydrogen (15 psi) atmosphere. After completion, the reaction mixture was filtered, washed with methanol (5 mL × 2) and concentrated to give 5-(cyclopropoxy)pyridin-2-amine (120 mg, 799 μmol, 72% yield) as a black oil which used for the next step without further purification. LCMS [M+1]⁺ = 151.1.

[0218] **Step 3:** To a solution of 5-(cyclopropoxy)pyridin-2-amine (120 mg, 799 μmol, 1.00 *eq.*) in methyl alcohol (2 mL) and water (1.0 mL) was added 2-chloroacetaldehyde (313 mg, 1.60 mmol, 257 μL, 2.00 *eq.*) and sodium bicarbonate (70.5 mg, 839 μmol, 1.05 *eq.*). The mixture was stirred at 70 °C for 2 hours. After such time the solvent was removed under reduced pressure, diluted with ethyl acetate (3 mL) and water (2 mL), and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 6-(cyclopropoxy)imidazo[1,2-*a*]pyridine (220 mg, crude) as a yellow solid which used for the next step without further purification. LCMS [M+1]⁺ = 175.2.

[0219] **Step 4:** To a solution of 6-(cyclopropoxy)imidazo[1,2-*a*]pyridine (220 mg, crude) in acetonitrile (2 mL) was added *N*-iodosuccinimide (313 mg, 1.39 mmol). The mixture was stirred at 20 °C for 1 hour. Upon completion the reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 20-80%) to give 6-(cyclopropoxy)-3-iodo-imidazo[1,2-*a*]pyridine, Intermediate AS (220 mg, 733 μmol, 58% yield) as a white solid. LCMS [M+1]⁺ = 300.9. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.03 (d, J = 2.0 Hz, 1H), 7.76 (s, 1H), 7.60 (d, J = 9.6 Hz, 1H), 7.17 (dd, J = 2.4, 9.6 Hz, 1H), 4.08 - 4.05 (m, 1H), 0.88 - 0.82 (m, 2H), 0.80 - 0.72 (m, 2H).

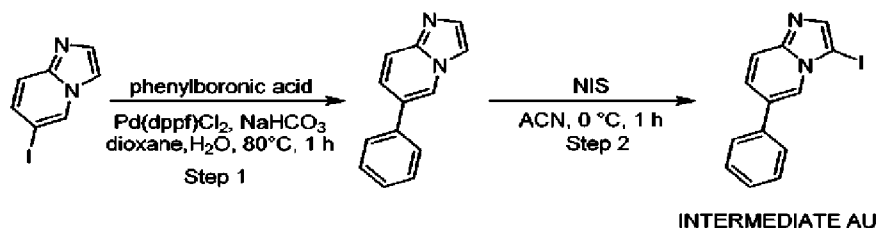
INTERMEDIATE AT



[0220] **Step 1:** To a solution of 5-(trifluoromethoxy)pyridin-2-amine (250 mg, 1.40 mmol, 1.00 *eq.*) in methanol (5 mL) and water (2.5 mL) was added 2-chloroacetaldehyde (289 mg, 1.47 mmol, 237 μ L, 1.05 *eq.*) and sodium bicarbonate (118 mg, 1.41 mmol, 54.8 μ L, 1.00 *eq.*). The mixture was stirred at 70 °C for 2 hours. The reaction mixture was then concentrated under reduced pressure and the residue diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 2). The combined organic layers were concentrated to give 6-(trifluoromethoxy)imidazo[1,2-*a*]pyridine (250 mg, crude) as a colorless oil which used for the next step without further purification.

[0221] **Step 2:** To a solution of 6-(trifluoromethoxy)imidazo[1,2-*a*]pyridine (238 mg, crude) in acetonitrile (10 mL) was added *N*-iodosuccinimide (291 mg, 1.30 mmol) in acetonitrile (5 mL) at 0 °C, and the resulting yellow suspension was allowed to warm to 20 °C for 2 hours. The reaction mixture was then diluted with water (10 mL), extracted with ethyl acetate (10 mL $\times$ 3) and the combined organic extracts were washed with brine (10 mL), dried, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate 10-15%) to give 3-iodo-6-(trifluoromethoxy)imidazo[1,2-*a*]pyridine, Intermediate AT (180 mg, 548 μ mol, 46% yield) as yellow solid. LCMS $[M+1]^+$ = 329.0. ^1H NMR (400 MHz, CDCl_3) δ = 8.23 - 8.19 (s, 1H), 7.80 (s, 1H), 7.71 (d, *J* = 9.6 Hz, 1H), 7.27 (m, 1H).

INTERMEDIATE AU

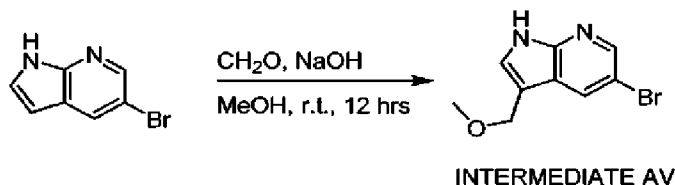


[0222] **Step 1:** A mixture of 6-iodoimidazo[1,2-*a*]pyridine (500 mg, 2.05 mmol, 1.00 *eq.*), phenylboronic acid (275 mg, 2.25 mmol, 1.10 *eq.*), $\text{Pd}(\text{dppf})\text{Cl}_2$ (150 mg, 205 μ mol, 0.10 *eq.*),

sodium bicarbonate (344 mg, 4.10 mmol, 159 μ L, 2.00 *eq.*) in dioxane (5 mL) and water (1.00 mL) was degassed with nitrogen and stirred at 80 °C for 1 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue diluted with ethyl alcohol (5 mL) and the solution was then concentrated. The residue was purified by prep-TLC (dichloromethane: methyl alcohol, 10%) to give 6-phenylimidazo[1,2-*a*]pyridine (250 mg, 1.29 mmol, 62% yield,) as a white solid. LCMS $[M+1]^+ = 195.1$.

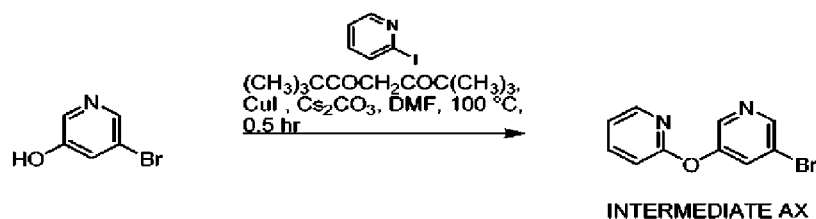
[0223] **Step 2:** To a solution of 6-phenylimidazo [1,2-*a*]pyridine (100 mg, 515 μ mol, 1.00 *eq.*) in acetonitrile (2 mL) was added *N*-iodosuccinimide (127 mg, 566 μ mol, 1.10 *eq.*) and the mixture was stirred at 0 °C for 1 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue diluted with ethyl alcohol (2 mL) and the supernatant removed and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate 10%) to give 3-iodo-6-phenyl-imidazo[1,2-*a*]pyridine, Intermediate AU (120 mg, 375 μ mol, 72% yield) as a yellow solid. LCMS $[M+1]^+ = 321.0$. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 8.40 (br s, 1H), 7.77 (m, 3H), 7.73 - 7.62 (m, 2H), 7.58 - 7.49 (m, 2H), 7.45 (m, 1H).

INTERMEDIATE AV



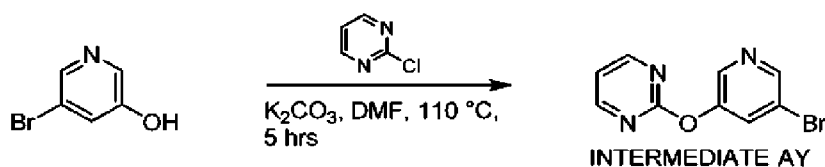
[0224] To a solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 10.2 mmol, 1.00 *eq.*) in methyl alcohol (10 mL) was added formaldehyde (610 mg, 20.3 mmol, 559 μ L, 2.00 *eq.*) and sodium hydroxide (812 mg, 20.3 mmol, 2.00 *eq.*) and the mixture was stirred at 20 °C for 2 hours. After completion the reaction mixture was then filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate 5-20%) then by prep-TLC (petroleum ether: ethyl acetate 20%) to give 5-bromo-3-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine, Intermediate AV (120 mg, 498 μ mol, 5% yield) as white solid. LCMS $[M+1]^+ = 243.0$. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 11.83 (br s, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 4.53 (s, 2H), 3.25 (s, 3H).

INTERMEDIATE AX



[0225] To a solution of 5-bromopyridin-3-ol (500 mg, 2.87 mmol, 1.00 *eq.*) in DMF (10 mL) was added cesium carbonate (1.87 g, 5.75 mmol, 2.00 *eq.*), 2-iodopyridine (707 mg, 3.45 mmol, 366 μ L, 1.20 *eq.*), 2,2,6,6-tetramethylheptane-3,5-dione (212 mg, 1.15 mmol, 237 μ L, 0.40 *eq.*) and cuprous iodide (109 mg, 575 μ mol, 0.20 *eq.*). The mixture was stirred at 100 °C for 0.5 hour. The reaction mixture was then diluted with water (100 mL) and extracted with ethyl acetate (70.0 mL $\times$ 3). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 0-20%) to give 3-bromo-5-(2-pyridyloxy)pyridine Intermediate AX (600 mg, 1.45 mmol, 50% yield) as a yellow oil. LCMS $[M+1]^+ = 250.8$. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.57 (d, *J* = 2.0 Hz, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 8.16 (ddd, *J* = 0.8, 2.0, 4.8 Hz, 1H), 8.02 (s, 1H), 7.91 (ddd, *J* = 2.0, 7.2, 8.0 Hz, 1H), 7.21 - 7.15 (m, 2H).

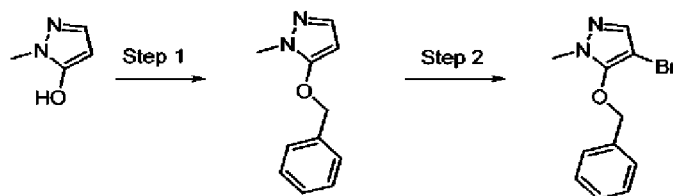
INTERMEDIATE AY



[0226] To a solution of 2-chloropyrimidine (300 mg, 2.62 mmol, 1.00 *eq.*) in DMF (2 mL) was added potassium carbonate (724 mg, 5.24 mmol, 2.00 *eq.*) and 5-bromopyridin-3-ol (479 mg, 2.75 mmol, 1.05 *eq.*). The mixture was stirred at 110 °C for 5 hours. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (80 mL $\times$ 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-[(5-bromo-3-pyridyl)oxy]pyrimidine, Intermediate AY (523 mg, crude) as a red solid and used into the next step directly without further purification. LCMS $[M+1]^+ = 252.0$; ¹H NMR (400 MHz,

DMSO-*d*₆) δ = 8.70 (s, 1H), 8.69 (s, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 8.17 (t, *J* = 2.0 Hz, 1H), 7.34 (t, *J* = 4.8 Hz, 1H).

INTERMEDIATE AY-1



INTERMEDIATE AY-1

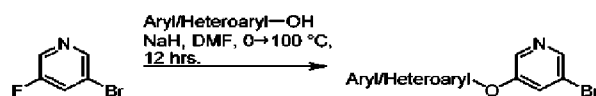
[0227] **Step 1:** To a solution of 2-methylpyrazol-3-ol (500 mg, 5.10 mmol, 1.00 *eq.*), (bromomethyl)benzene (1.05 g, 6.12 mmol, 726 μ L, 1.20 *eq.*) in DMF (6.00 mL) was added potassium carbonate (1.06 g, 7.65 mmol, 1.50 *eq.*). The mixture was stirred at 120 °C for 4 hours. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 50/1 to 6/1) to give 5-benzyloxy-1-methyl-pyrazole (450 mg, 2.39 mmol, 47% yield) as a colorless oil. LCMS $[M+1]^+ = 189.2$; ¹H NMR (400 MHz, CDCl₃) δ = 7.43 - 7.41 (m, 3H), 7.40 - 7.35 (m, 2H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.24 - 7.21 (d, *J* = 2.0 Hz, 1H), 5.08 (s, 2H), 3.67 (s, 3H).

[0228] **Step 2:** To a solution of 5-benzyloxy-1-methyl-pyrazole (400 mg, 2.13 mmol, 1.00 *eq.*) in acetonitrile (6 mL) was added NBS (416 mg, 2.34 mmol, 1.10 *eq.*). The mixture was stirred at 0 °C for 0.5 hours. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 20/1) to give 5-benzyloxy-4-bromo-1-methyl-pyrazole (320 mg, 1.20 mmol, 56% yield) as a yellow oil. LCMS $[M+1]^+ = 266.9$; ¹H NMR (400 MHz, CDCl₃) δ = 7.39 (s, 5H), 7.32 (s, 1H), 5.28 (s, 2H), 3.45 (s, 3H).

[0229] Intermediate AY-2 shown in Table I-IIb was prepared following the teachings of the General Reaction Schemes and the method to prepare Intermediate AY-1.

Table I-IIIb		
Intermediate	Structure	Spectral Data
AY-2		4-bromo-5-(cyclopropylmethoxy)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 233.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.32 - 7.28 (s, 1H), 4.11 - 4.07 (m, 2H), 3.74 - 3.68 (s, 3H), 1.25 - 1.16 (m, 1H), 0.67 - 0.57 (m, 2H), 0.37 - 0.28 (m, 2H)

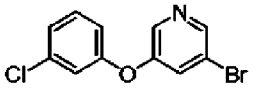
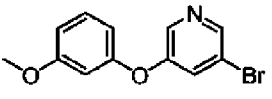
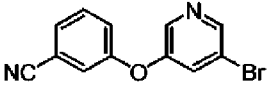
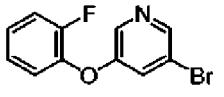
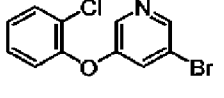
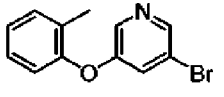
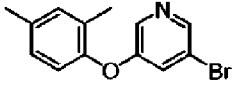
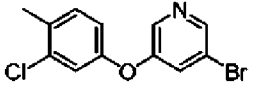
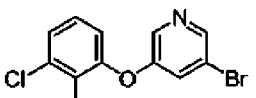
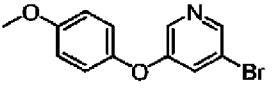
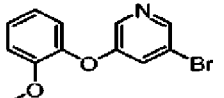
GENERAL PROCEDURE FOR INTERMEDIATES B-1 to B-15

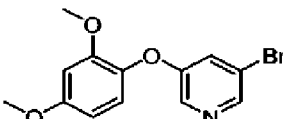


[0230] To the corresponding aryl/heteroaryl phenol (3.89 mmol, 1.00 *eq.*) in DMF (10 mL) was added sodium hydride (4.28 mmol, 60% purity, 1.10 *eq.*) at 0 °C under nitrogen. After the addition was complete the mixture was stirred at 25 °C for 0.5 hour, followed by addition with 3-bromo-5-fluoro-pyridine (3.89 mmol, 1.00 *eq.*) and stirred at 100 °C for a further 12 hours. After such time the reaction mixture was quenched by the addition water (10 mL) and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was used directly in the next step without further purification.

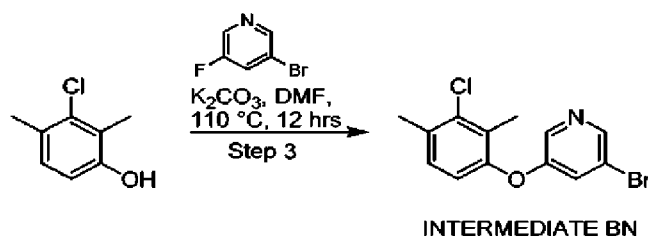
[0231] Following the teachings of the General Reaction Schemes and the general procedure for Intermediates B-1 to B-15 the intermediates in Table I-III were prepared.

Intermediate	Structure	Characterization
B-1		3-Bromo-5-(pyridin-3-yloxy)pyridine LCMS [M+1] ⁺ = 250.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.51 - 8.48 (m, 2H), 8.48 - 8.45 (m, 1H), 8.36 (d, <i>J</i> = 2.8 Hz, 1H), 7.47 (t, <i>J</i> = 2.0 Hz, 1H), 7.40 - 7.35 (m, 2H)
B-2		3-Bromo-5-(3-fluorophenoxy)pyridine LCMS [M+1] ⁺ = 268.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.53 (d, <i>J</i> = 1.6 Hz, 1H), 8.41 (d, <i>J</i> = 2.4 Hz, 1H), 7.81 (t, <i>J</i> = 2.0 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.08 - 7.03 (m, 2H), 6.97 - 6.92 (m, 1H)
B-3		3-Bromo-5-(m-tolyloxy)pyridine LCMS [M+1] ⁺ = 265.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.40 (d, <i>J</i> = 2.0 Hz, 1H), 8.33 (d, <i>J</i> = 2.4 Hz, 1H), 7.41 (t, <i>J</i> = 2.0 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.03 (d, <i>J</i> = 7.6 Hz, 1H), 6.92 - 6.81 (m, 2H), 2.37 (s, 3H)

B-4		3-Bromo-5-(3-chlorophenoxy)pyridine LCMS [M+1] ⁺ = 286.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.53 (d, J = 1.6 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.82 (q, J = 2.4 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.31 - 7.23 (m, 2H), 7.11 - 7.06 (m, 1H)
B-5		3-Bromo-5-(3-methoxyphenoxy)pyridine LCMS [M+1] ⁺ = 279.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.42 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 2.4 Hz, 1H), 7.44 (t, J = 2.4 Hz, 1H), 7.30 (t, J = 8.4 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.64 - 6.59 (m, 2H), 3.81 (s, 3H)
B-6		3-((5-Bromopyridin-3-yl)oxy)benzonitrile LCMS [M+1] ⁺ = 277.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.55 (d, J = 1.6 Hz, 1H), 8.43 (d, J = 2.4 Hz, 1H), 7.86 (t, J = 2.4 Hz, 1H), 7.69 - 7.66 (m, 2H), 7.62 (t, J = 8.4 Hz, 1H), 7.47 (ddd, J = 1.2, 2.4, 8.0 Hz, 1H)
B-7		3-Bromo-5-(2-fluorophenoxy)pyridine LCMS [M+1] ⁺ = 269.9; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.50 (d, J = 1.6 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 7.70 (t, J = 2.0 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.36 - 7.27 (m, 3H)
B-8		3-Bromo-5-(2-chlorophenoxy)pyridine LCMS [M+1] ⁺ = 286.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.49 (d, J = 1.6 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.66 - 7.62 (m, 2H), 7.43 (td, J = 1.6, 8.0 Hz, 1H), 7.34 - 7.28 (m, 2H)
B-9		3-Bromo-5-(o-tolyl)oxy)pyridine LCMS [M+1] ⁺ = 266.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.37 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 0.8, 7.2 Hz, 1H), 7.29 (s, 1H), 7.27 - 7.22 (td, J = 1.6, 7.6 Hz, 1H), 7.20 - 7.14 (td, J = 1.2, 7.6 Hz, 1H), 6.96 (dd, J = 1.2, 8.0 Hz, 1H), 2.23 (s, 3H)
B-10		3-Bromo-5-(2,4-dimethylphenoxy)pyridine LCMS [M+1] ⁺ = 278.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.35 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.26 - 7.24 (t, J = 2.4 Hz, 1H), 7.10 (s, 1H), 7.04 (dd, J = 1.2, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 2.35 (s, 3H), 2.17 (s, 3H)
B-11		3-Bromo-5-(3-chloro-4-methylphenoxy)pyridine LCMS [M+1] ⁺ = 299.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.43 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.44 - 7.41 (t, J = 2.4, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 1.6, 4.4 Hz, 1H), 2.38 (s, 3H).
B-12		3-Bromo-5-(3-chloro-2-methylphenoxy)pyridine LCMS [M+1] ⁺ = 299.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.41 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.32 - 7.31 (t, J = 2.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.88 (dd, J = 0.8, 8.0 Hz, 1H), 6.69 (dd, J = 1.6, 7.6 Hz, 1H), 2.31 (s, 3H)
B-13		3-Bromo-5-(4-methoxyphenoxy)pyridine LCMS [M+1] ⁺ = 280.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.36 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.35 - 7.33 (m, 1H), 7.04 - 6.99 (m, 2H), 6.96 - 6.91 (m, 2H), 3.84 (s, 3H)
B-14		3-Bromo-5-(2-methoxyphenoxy)pyridine LCMS [M+1] ⁺ = 280.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.35 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 2.0, 2.4 Hz, 1H), 7.08 - 7.01 (m, 2H), 6.95 - 6.86 (m, 2H), 3.82 (s, 3H)

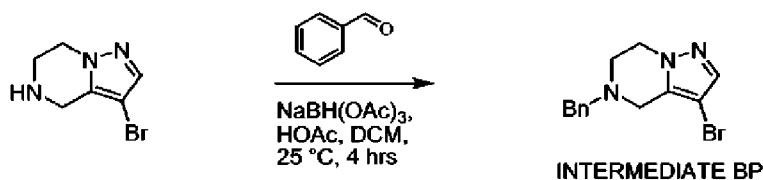
B-15		3-bromo-5-(2,4-dimethoxyphenoxy)pyridine LCMS $[M+1]^+ = 312.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.32$ (d, $J = 1.6$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.24 (t, $J = 2.0$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 1H), 6.60 (d, $J = 2.8$ Hz, 1H), 6.49 (dd, $J = 2.8$, 8.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H)

INTERMEDIATE BN



[0232] To a solution of 3-bromo-5-fluoro-pyridine (210 mg, 1.19 mmol, 0.95 *eq.*) in DMF (10 mL) was added potassium carbonate (347 mg, 2.51 mmol, 2.00 *eq.*) and 3-chloro-2, 4-dimethyl-phenol (197 mg, 1.26 mmol, 1.00 *eq.*). The mixture was stirred at 110 °C for 12 hours. After such time the reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were then washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether:ethyl acetate 0-20%) to give 3-bromo-5-(3-chloro-2, 4-dimethyl-phenoxy) pyridine, Intermediate BN (178 mg, 569 μmol , 45% yield) as a colorless oil. LCMS $[M+1]^+ = 314.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 8.45$ (d, $J = 2.0$ Hz, 1H), 8.31 (d, $J = 2.4$ Hz, 1H), 7.57 (t, $J = 2.0$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H).

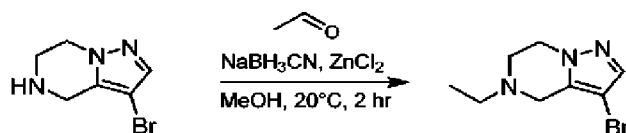
INTERMEDIATE BP



[0233] To a solution of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (300 mg, 949 μmol , 1.00 *eq.*, TFA) and benzaldehyde (131 mg, 1.23 mmol, 125 μL , 1.30 *eq.*) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (402 mg, 1.90 mmol, 2.00 *eq.*) and acetic acid (114 mg, 1.90 mmol, 109 μL , 2.00 *eq.*). The mixture was then stirred at

25 °C for 4 hours. After such time the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 25%) to give 5-benzyl-3-bromo-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine, Intermediate BP (170 mg, 582 μ mol, 61% yield) as a colorless oil. LCMS $[M+1]^+ = 294.0$. ¹H NMR (400 MHz, CD₃OD) δ = 7.45 (s, 1H), 7.41 - 7.32 (m, 5H), 4.12 (t, *J* = 5.6 Hz, 2H), 3.77 (s, 2H), 3.57 (s, 2H), 2.96 (t, *J* = 5.6 Hz, 2H).

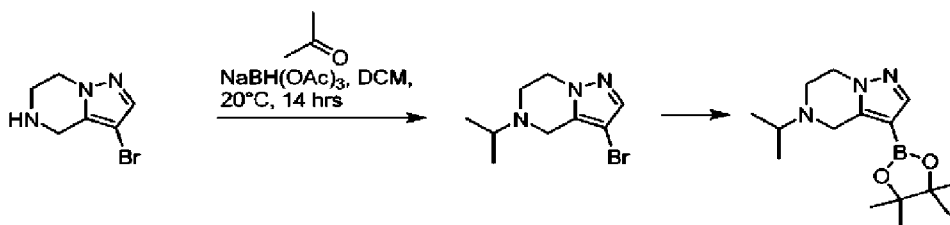
INTERMEDIATE BQ



INTERMEDIATE BQ

[0234] A mixture of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (400 mg, 1.27 mmol, 1.00 *eq.*), acetaldehyde (5.0 M, 508 μ L, 2.01 *eq.*), sodium cyanoborohydride (160 mg, 2.54 mmol, 2.01 *eq.*), zinc chloride (1.0 M, 2.53 mL, 2.00 *eq.*) in methanol (8 mL) was stirred at 25 °C for 2 hours. After such time the solvent was evaporated and the residue purified by column chromatography (SiO₂, dichloromethane: methanol 0-10%). The product was further purified by prep-HPLC (Waters Xbridge C18 150 $\times$ 50 mm $\times$ 10 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 16%-46%, 11.5 min) to give 3-bromo-5-ethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine, intermediate BQ (100 mg, 434 μ mol, 34% yield) as an colorless oil. ¹H NMR (400 MHz, CD₃OD) δ = 7.47 (s, 1H), 4.21 - 4.11 (t, *J* = 6.0 Hz, 2H), 3.61 (s, 2H), 3.03 - 2.94 (t, *J* = 6.0 Hz, 2H), 2.69 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H).

INTERMEDIATE BR

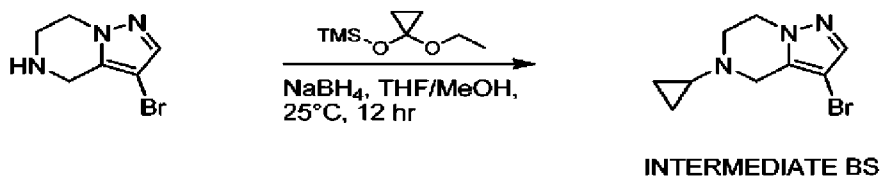


INTERMEDIATE BR

[0235] **Step 1:** To a mixture of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (200 mg, 990 μ mol, 1.00 *eq.*) and acetone (862 mg, 14.9 mmol, 1.09 mL, 15.0 *eq.*) in dichloromethane (1.00 mL), was added sodium triacetoxyborohydride (420 mg, 1.98 mmol, 2.00 *eq.*). After stirring at 25 °C for 14 hours the mixture was extracted with dichloromethane (5 mL $\times$ 3), washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 10%) to give 3-bromo-5-isopropyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine (150 mg, 531 μ mol, 54% yield) as a yellow oil. LCMS $[M+1]^+ = 244.0$. ¹H NMR (400 MHz, CDCl₃) δ = 7.35 (s, 1H), 4.12 - 4.06 (t, *J* = 5.2 Hz, 2H), 3.59 (s, 2H), 2.96 - 2.90 (m, 1H), 2.89 - 2.86 (t, *J* = 5.2 Hz, 2H), 1.09 (s, 3H), 1.07 (s, 3H).

[0236] **Step 2:** A mixture of 3-bromo-5-isopropyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine (80.0 mg, 328 μ mol, 1.00 *eq.*), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (166 mg, 655 μ mol, 2.00 *eq.*), potassium acetate (113 mg, 1.15 mmol, 3.50 *eq.*) and PdCl₂[P(Cy)₃]₂ (24.2 mg, 32.8 μ mol, 0.10 *eq.*) in dimethylaminopyridine (1 mL) was purged with nitrogen then stirred at 90 °C for 20 hours. The mixture was then concentrated under reduced pressure to give 5-isopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine, Intermediate BR (700 mg, 303 μ mol, 92% yield) as a black solid. LCMS $[M+1]^+ = 292.2$.

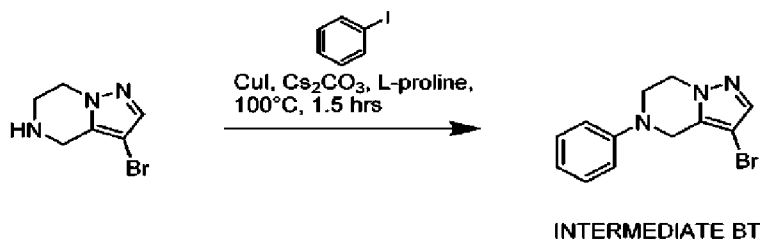
INTERMEDIATE BS



[0237] A pressure tube was charged with 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (260 mg, 1.29 mmol, 1.00 *eq.*), (1-ethoxycyclopropoxy)trimethylsilane (673 mg, 3.86 mmol, 776 μ L, 3.00 *eq.*), sodium cyanoborohydride (243 mg, 3.86 mmol, 3.00 *eq.*) and acetic acid (773 mg, 12.9 mmol, 736 μ L, 10.0 *eq.*) in THF (5 mL) and ethyl alcohol (5 mL). The resulting solution was stirred for 2 hours at 60 °C, then the reaction mixture was concentrated to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate 20%) to give 3-bromo-5-cyclopropyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine, Intermediate BS (150 mg, 620 μ mol, 48% yield) as yellow solid. ¹H NMR

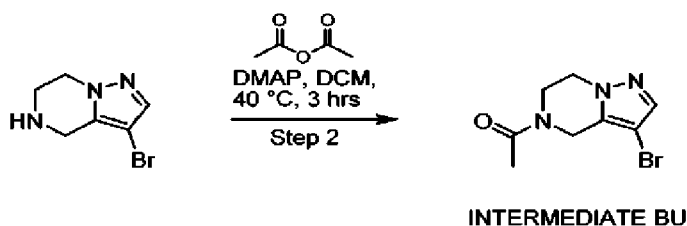
(400MHz, CD₃OD) δ = 7.45 (s, 1H), 4.14 - 4.09 (m, 2H), 3.75 (s, 2H), 3.20 - 3.10 (m, 2H), 2.02 - 1.96 (m, 1H), 0.65 - 0.57 (m, 2H), 0.56 - 0.44 (m, 2H).

INTERMEDIATE BT



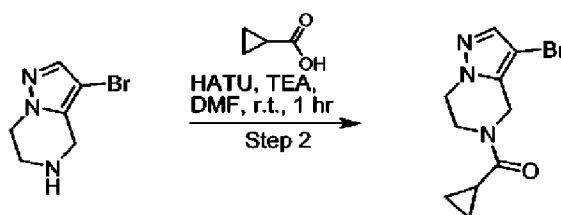
[0238] A mixture of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (500 mg, 1.58 mmol, 1.00 *eq.*), iodobenzene (1.29 g, 6.33 mmol, 705 μ L, 4.00 *eq.*), copper iodide (60.3 mg, 316 μ mol, 0.20 *eq.*), (2*S*)-pyrrolidine-2-carboxylic acid (72.9 mg, 633 μ mol, 0.40 *eq.*) and cesium carbonate (1.03 g, 3.16 mmol, 2.00 *eq.*) in DMF (10 mL) was degassed and purged with nitrogen then stirred at 100 °C for 1.5 hours. After such time the mixture was cooled, extracted with ethyl acetate (5 mL $\times$ 3), washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The formed residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 5-10%) to give 3-bromo-5-phenyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine, Intermediate BT (55 mg, 197 μ mol, 12% yield) as yellow solid. LCMS $[M+1]^+ = 278.2$.

INTERMEDIATE BU



[0239] A mixture of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (200 mg, 633 μ mol, 1.00 *eq.*), acetyl acetate (96.9 mg, 949 μ mol, 88.9 μ L, 1.50 *eq.*) and DMAP (7.73 mg, 63.3 μ mol, 0.10 *eq.*) in dichloromethane (10 mL) was degassed and purged with nitrogen then stirred at 40 °C for 3 hours. Upon completion the reaction mixture was concentrated under reduced pressure to give 1-(3-bromo-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazin-5-yl)ethanone, Intermediate BU (100 mg, crude) as a white solid. LCMS $[M+1]^+ = 244.2$.

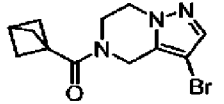
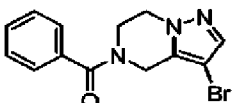
INTERMEDIATE BV



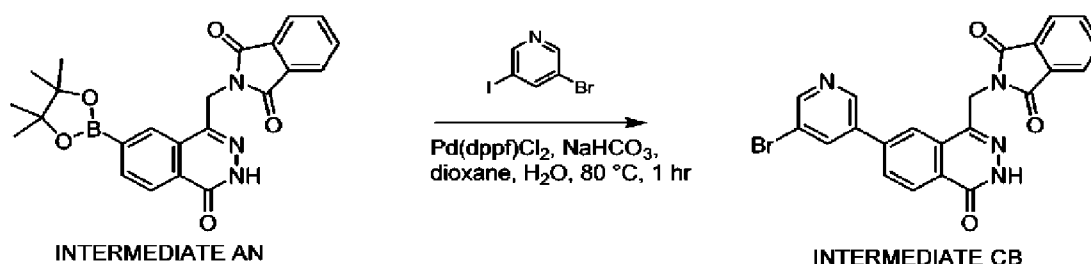
[0240] To a solution of 3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (250 mg, 791 μmol , 1.00 *eq.*) in dimethylformamide (2 mL) was added triethylamine (240 mg, 2.37 mmol, 330 μL , 3.00 *eq.*), HATU (601 mg, 1.58 mmol, 2.00 *eq.*), and cyclopropane carboxylic acid (102 mg, 1.19 mmol, 93.7 μL , 1.50 *eq.*). The mixture was stirred at 35 °C for 1 hour. After such time the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (30.0 mL $\times$ 3) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The formed residue was purified by column chromatography (SiO₂, petroleum ether:ethyl acetate 0-50%) to give (3-bromo-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazin-5-yl)-cyclopropyl-methanone, Intermediate BV (139 mg, 515 μmol , 65% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.48 (s, 1H), 4.89 - 4.68 (m, 2H), 4.33 - 4.05 (m, 4H), 1.87 - 1.79 (m, 1H), 1.09 - 1.04 (m, 2H), 0.93 - 0.84 (m, 2H).

[0241] Following the teachings of the General Reaction Schemes, and the procedure for INTERMEDIATE BV, INTERMEDIATES C-1 to C-5 were prepared as shown in Table I-IV:

Table I-IV		
Intermediate	Structure	Characterization
C-1		(3-Bromo-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)(cyclobutyl)methanone LCMS [M+1] ⁺ = 286.1 ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.59 (s, 1H), 4.60 - 4.49 (m, 2H), 4.14 - 4.05 (m, 2H), 3.96 - 3.79 (m, 2H), 3.55 - 3.47 (m, 1H), 2.25 - 2.10 (m, 4H), 1.98 - 1.88 (m, 1H), 1.81 - 1.70 (m, 1H)
C-2		(3-Bromo-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)(cyclopentyl)methanone LCMS [M+1] ⁺ = 297.9
C-3		(3-Bromo-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)(cyclohexyl)methanone ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.59 (s, 1H), 4.78 - 4.50 (m, 2H), 4.16 (m, 1H), 4.06 - 3.91 (m, 3H), 2.79 - 2.70 (m, 1H), 1.77 - 1.58 (m, 5H), 1.44 - 1.17 (m, 5H)

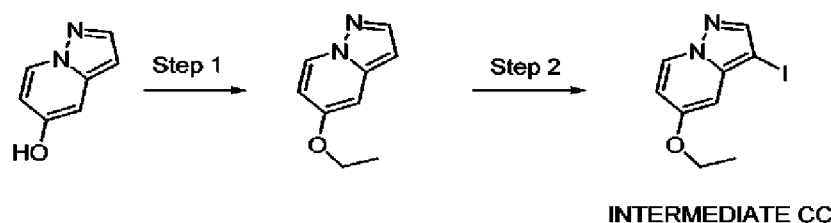
C-4		bicyclo[1.1.1]pentan-1-yl(3-bromo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone LCMS [M+1] ⁺ = 298.1
C-5		(3-bromo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)(phenyl)methanone LCMS [M+1] ⁺ = 308.0

INTERMEDIATE CB



[0242] A mixture of 3-bromo-5-iodo-pyridine (3.00 g, 10.6 mmol, 1.00 *eq.*), intermediate AN (2.28 g, 5.28 mmol, 0.50 *eq.*), sodium bicarbonate (1.78 g, 21.1 mmol, 822 μ L, 2.00 *eq.*), Pd(dppf)Cl₂ (773 mg, 1.06 mmol, 0.10 *eq.*) in dioxane (50 mL) and water (10 mL) was degassed with nitrogen 3 then stirred at 80 °C for 1 hour. The cooled reaction mixture was then concentrated under reduced, diluted with water (200 mL), filtered and the filter cake was triturated with dichloromethane: methyl alcohol (10%, 150 mL). The solid was filtered, dried and the solid was triturated a second time in methyl alcohol (100 mL), then filtered and dried to give 2-[[7-(5-bromo-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione, Intermediate CB (775 mg, crude) as a gray solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.54 (s, 1H), 9.16 (d, *J* = 1.2 Hz, 1H), 8.82 (d, *J* = 1.6 Hz, 1H), 8.73 (s, 1H), 8.52 (s, 1H), 8.38 - 8.28 (m, 2H), 7.98 - 7.95 (m, 2H), 7.90 (m, 2H), 5.38 (s, 2H).

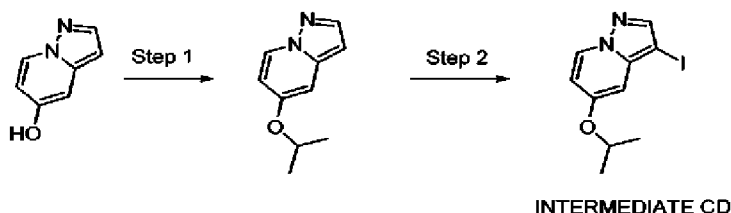
INTERMEDIATE CC



[0243] **Step 1:** To a solution of pyrazolo[1,5-*a*]pyridin-5-ol (250 mg, 1.86 mmol, 1.00 *eq.*) in DMF (2 mL) was added potassium carbonate (773 mg, 5.59 mmol, 3.00 *eq.*) and the mixture stirred at 30 °C for 0.5 hour. Iodoethane (872 mg, 5.59 mmol, 447 μ L, 3.00 *eq.*) was then added and the resulting mixture stirred at 30 °C for 12 hours. After such time the reaction mixture was diluted with water (50 mL) extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate 20%) to give 5-ethoxypyrazolo[1,5-*a*]pyridine (272 mg, 1.68 mmol, 90% yield) as a white solid. LCMS $[M+1]^+ = 163.2$; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.50 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.52 (dd, *J* = 2.8, 7.6 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 2H), 1.35 (t, *J* = 6.8 Hz, 3H).

[0244] **Step 2:** To a solution of 5-ethoxypyrazolo[1,5-*a*]pyridine (260 mg, 1.60 mmol, 1.00 *eq.*) in acetonitrile (1.0 mL) was added NIS (397 mg, 1.76 mmol, 1.10 *eq.*). The mixture was stirred at 25 °C for 1 hour before the mixture was diluted with water (30 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate 20%) to give 5-ethoxy-3-iodo-pyrazolo[1,5-*a*]pyridine (369 mg, 1.28 mmol, 80% yield) as a pink solid. LCMS $[M+1]^+ = 289.1$; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.57 (d, *J* = 7.6 Hz, 1H), 7.96 (s, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 2.4, 7.6 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 1.37 (t, *J* = 6.8 Hz, 3H).

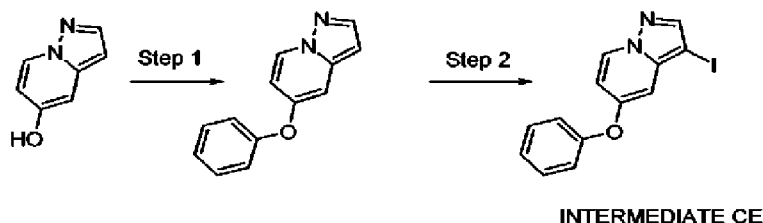
INTERMEDIATE CD



[0245] Intermediate CD, 3-iodo-5-isopropoxy-pyrazolo[1,5-*a*]pyridine was prepared as a yellow solid (299 mg, 0.99 mmol, 87% yield over 2 steps) using 2-iodopropane following the same procedure as used for the preparation of Intermediate CC. LCMS $[M+1]^+ = 303.0$; ¹H

NMR (400 MHz, DMSO-*d*₆) δ = 8.56 (d, *J* = 7.6 Hz, 1H), 7.96 (s, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 6.57 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.77 (td, *J* = 6.0, 12.0 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H).

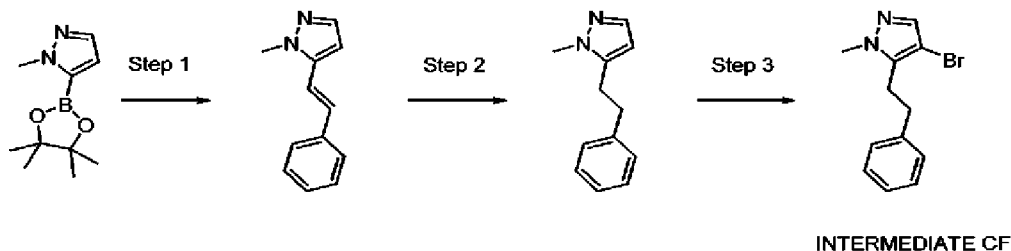
INTERMEDIATE CE



[0246] **Step 1:** A mixture of pyrazolo[1,5-*a*]pyridin-5-ol (300 mg, 2.24 mmol, 1.00 *eq.*), phenylboronic acid (545 mg, 4.47 mmol, 2.00 *eq.*), 4Å MS (30 mg), copper acetate (812 mg, 4.47 mmol, 2.00 *eq.*) and triethylamine (1.13 g, 11.2 mmol, 1.56 mL, 5.00 *eq.*) in dichloromethane (10 mL) was degassed with oxygen and stirred at 25 °C for 10 hours under an oxygen (15 psi) atmosphere. After such time the reaction mixture was filtered, concentrated and the formed residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 0-20%) to give 5-phenoxy-pyrazolo[1,5-*a*]pyridine (200 mg, 0.95 mmol, 43% yield) as a yellow oil. LCMS [M+1]⁺ = 211.2.

[0247] **Step 2:** To a solution of 5-phenoxy-pyrazolo[1,5-*a*]pyridine (180 mg, 0.86 mmol, 1.00 *eq.*) in acetonitrile (2 mL) was added NIS (212 mg, 0.94 mmol, 1.10 *eq.*). The mixture was stirred at 0 °C for 1 hour. The reaction mixture was then concentrated and the residue purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 0-5%) to give 3-iodo-5-phenoxy-pyrazolo[1,5-*a*]pyridine (170 mg, 0.51 mmol, 59% yield) as a yellow oil. LCMS [M+1]⁺ = 336.9.

INTERMEDIATE CF



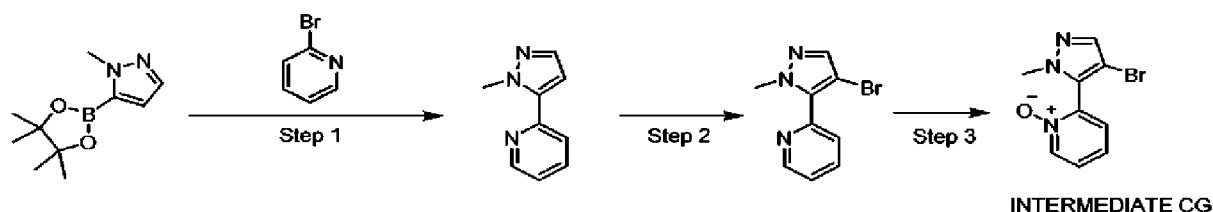
[0248] **Step 1:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.50 g, 7.21 mmol, 1.00 *eq.*), [(*E*)-2-bromovinyl]benzene (2.90 g, 15.8 mmol,

2.03 mL, 2.20 *eq.*), Pd(PPh₃)₂Cl₂ (506 mg, 721 μ mol, 0.10 *eq.*), potassium carbonate (1.30 g, 9.41 mmol, 1.30 *eq.*) in ethyl alcohol (3.8 mL) and DMF (7.5 mL) was degassed with nitrogen and then stirred at 75 °C for 2 hours. After such time the mixture was cooled to ambient temperature, diluted with water (100 mL) and extracted with ethyl acetate (80 mL $\times$ 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate 0-20%) to give 1-methyl-5-[(*E*)-styryl]pyrazole (990 mg, 5.37 mmol, 74% yield) as a yellow solid. LCMS [M+1]⁺ = 185.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.65 (d, *J* = 7.2 Hz, 2H), 7.42 - 7.36 (m, 3H), 7.32 - 7.25 (m, 2H), 7.12 (d, *J* = 16.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 3.91 (s, 3H).

[0249] **Step 2:** To a solution of 1-methyl-5-[(*E*)-styryl]pyrazole (400 mg, 2.17 mmol, 1.00 *eq.*) in ethyl alcohol (3 mL) was added Pd/C (10.0 mg, 10% Pd) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times and the mixture was then stirred under hydrogen (15.0 psi) at 25 °C for 12 hours. After such time the reaction mixture was filtered and concentrated under reduced pressure to give 1-methyl-5-(2-phenylethyl)pyrazole (385 mg, 1.93 mmol, 89% yield) as a yellow oil and used into the next step without further purification. LCMS [M+1]⁺ = 187.2.

[0250] **Step 3:** To a solution of 1-methyl-5-(2-phenylethyl)pyrazole (385 mg, 1.93 mmol, 1.00 *eq.*) in acetonitrile (10 mL) was added *N*-bromosuccinimide (343 mg, 1.93 mmol, 1.00 *eq.*). The mixture was then stirred at 0 °C for 0.5 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue purified by prep-TLC (SiO₂, Petroleum ether/ethyl acetate 20%) to give 4-bromo-1-methyl-5-(2-phenylethyl)pyrazole (430 mg, 1.62 mmol, 84% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.43 (s, 1H), 7.31 - 7.24 (m, 2H), 7.23 - 7.18 (m, 1H), 7.17 - 7.11 (m, 2H), 3.58 (s, 3H), 2.97 - 2.89 (t, *J* = 7.2 Hz, 2H), 2.84 - 2.77 (t, *J* = 7.2 Hz, 2H).

INTERMEDIATE CG

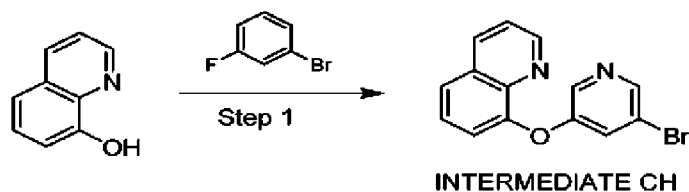


[0251] **Step 1:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.00 g, 4.81 mmol, 1.00 *eq.*), 2-bromopyridine (911 mg, 5.77 mmol, 0.55 mL, 1.20 *eq.*), cesium carbonate (3.13 g, 9.61 mmol, 2.00 *eq.*) and Pd(dppf)Cl₂ (352 mg, 0.48 mmol, 0.10 *eq.*) in dioxane (10 mL) and water (2 mL) was degassed and purged with nitrogen and then the mixture was stirred at 100 °C for 1 hour. After such time the cooled reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 0-20%) to give 2-(2-methylpyrazol-3-yl)pyridine (860 mg, crude) as a red oil which used into the next step directly without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.69 - 8.66 (m, 1H), 7.89 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.78 (td, *J* = 1.2, 8.0 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.37 (ddd, *J* = 1.2, 4.8, 7.6 Hz, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 4.14 (s, 3H).

[0252] **Step 2:** To a solution of 2-(2-methylpyrazol-3-yl)pyridine (760 mg, crude) in acetonitrile (10 mL) was added *N*-bromosuccinimide (850 mg, 4.77 mmol). The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was then concentrated under reduced pressure and the residue purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate 20%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)pyridine (507 mg, 2.13 mmol, 44% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.77 (td, *J* = 0.8, 4.0 Hz, 1H), 8.01 (dt, *J* = 2.0, 7.6 Hz, 1H), 7.76 –

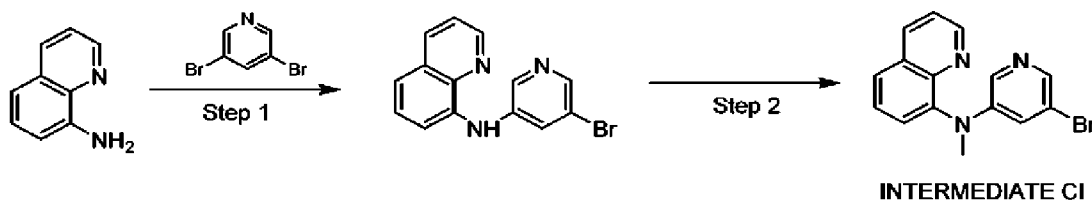
[0253] **Step 3:** To a solution of 2-(4-bromo-2-methyl-pyrazol-3-yl)pyridine (150 mg, 0.63 mmol, 1.00 *eq.*) in dichloroethane (3 mL) was added meta-chloroperbenzoic acid (435 mg, 2.14 mmol, 85% purity, 3.40 *eq.*). The mixture was stirred at 60 °C for 5 hours. The reaction mixture was then quenched by addition saturated sodium sulfite solution (20 mL) and extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate 50%) to give 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)pyridine 1-oxide (185 mg, crude) as a yellow solid, which was used into the next step directly without further purification. LCMS [M+1]⁺ = 254.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.46 (d, *J* = 6.4 Hz, 1H), 7.70 (s, 1H), 7.5 (dt, *J* = 1.2, 7.6 Hz, 2H), 7.52 - 7.47 (m, 1H), 3.74 (s, 3H).

INTERMEDIATE CH



[0254] **Step 1:** A mixture of quinolin-8-ol (454 mg, 3.13 mmol, 0.54 mL, 1.10 *eq.*), 3-bromo-5-fluoropyridine (500 mg, 2.84 mmol, 1.00 *eq.*), potassium carbonate (785 mg, 5.68 mmol, 2.00 *eq.*) in DMF (6 mL) was degassed with nitrogen then stirred at 110 °C for 3 hours. After such time the mixture was extracted with ethyl acetate (5 mL $\times$ 3) and the combined extracts were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 8-[(5-bromo-3-pyridyl)oxy]quinoline (0.30 g, 0.75 mmol, 26% yield) as a yellow oil. LCMS $[M+1]^+ = 301.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.95$ (dd, $J = 2.0, 4.0$ Hz, 1H), 8.43 (d, $J = 2.0$ Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H), 8.25 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.73 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.50 (dd, $J = 4.0, 8.4$ Hz, 1H), 7.47 - 7.43 (m, 2H).

INTERMEDIATE CI

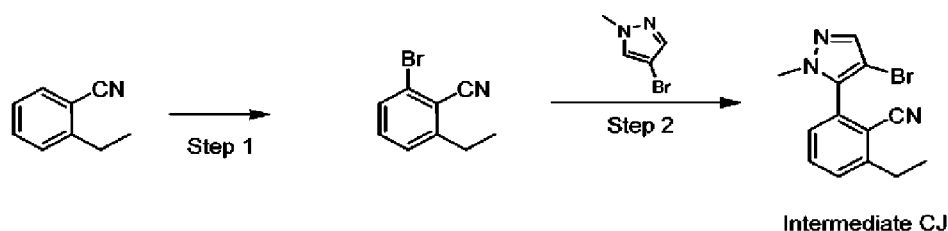


[0255] **Step 1:** A mixture of 3,5-dibromopyridine (1.48 g, 6.25 mmol, 1.00 *eq.*), quinolin-8-amine (901 mg, 6.25 mmol, 1.00 *eq.*), sodium *tert*-butoxide (901 mg, 9.37 mmol, 1.50 *eq.*), $\text{Pd}_2(\text{dba})_3$ (57.2 mg, 62.5 μmol , 0.01 *eq.*) and Xantphos (72.3 mg, 125 μmol , 0.02 *eq.*) in dioxane (10 mL) was degassed with nitrogen then stirred at 100 °C for 2 hours. After such time the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by reversed-phase HPLC (0.1% formic acid (FA) condition) to give *N*-(5-bromo-3-pyridyl)quinolin-8-amine (160 mg, 486 μmol , 7% yield) as a yellow solid. LCMS $[M+1]^+ = 300.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.82$ (dd, $J = 1.6, 4.0$ Hz, 1H), 8.61 (d, $J = 2.4$ Hz, 1H), 8.40 (br s, 1H), 8.31 (d, $J = 1.6$ Hz, 1H), 8.17

(dd, $J = 1.6, 8.4$ Hz, 1H), 7.92 (t, $J = 2.0$ Hz, 1H), 7.51 - 7.46 (m, 3H), 7.37 (dd, $J = 1.6, 8.0$ Hz, 1H).

[0256] **Step 2:** *N*-(5-bromo-3-pyridyl)quinolin-8-amine (130 mg, 394 μ mol, 1.00 *eq.*) was dissolved in DMF (2 mL), then sodium hydride (32 mg, 790 μ mol, 60.0% purity, 2.00 *eq.*) was added at 0 °C and the mixture was stirred at 0 °C for 10 minutes. After such time methyl iodide (224 mg, 1.58 mmol, 98 μ L, 4.00 *eq.*) was added and the resulting mixture was stirred at 20 °C for 1 hour. The reaction mixture was then quenched with water (10 mL), extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give *N*-(5-bromo-3-pyridyl)-*N*-methyl-quinolin-8-amine (150 mg, 334 μ mol, 85% yield) as a yellow oil. LCMS $[M+1]^+ = 314.1$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.90$ (dd, $J = 1.6, 4.4$ Hz, 1H), 8.24 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.01 (d, $J = 2.0$ Hz, 1H), 7.92 (d, $J = 2.8$ Hz, 1H), 7.82 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.65 - 7.62 (m, 1H), 7.61 - 7.57 (m, 1H), 7.46 (dd, $J = 4.4, 8.4$ Hz, 1H), 7.10 (t, $J = 2.4$ Hz, 1H), 3.49 (s, 3H).

INTERMEDIATE CJ



[0257] **Step 1:** A mixture of 2-ethylbenzonitrile (500 mg, 3.81 mmol, 0.51 mL, 1.00 *eq.*), *p*-toluenesulfonic acid (363 mg, 1.91 mmol, 0.50 *eq.*), *N*-Bromosuccinimide (746 mg, 4.19 mmol, 1.10 *eq.*) and palladium acetate (85.6 mg, 0.38 mol, 0.10 *eq.*) in 1,2-dichloroethane (10 mL) was degassed with nitrogen then stirred at 70 °C for 12 hours. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 0-5%) to give 2-bromo-6-ethylbenzonitrile (446 mg, 1.15 mmol, 30% yield) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 7.76$ (dd, $J = 0.8, 7.6$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.60 - 7.54 (m, 1H), 2.81 (m, 2H), 1.22 (m, 3H).

[0258] **Step 2:** A mixture of 2-bromo-6-ethylbenzonitrile (446 mg, 1.15 mmol, 1.00 *eq.*), 4-bromo-1-methylpyrazole (203 mg, 1.26 mmol, 1.10 *eq.*), palladium acetate (2.57 mg, 0.12

mmol, 0.01 *eq.*), DavePhos (9.0 mg, 0.23 mmol, 0.02 *eq.*), 2-methylpropanoic acid (30.3 mg, 0.34 mmol, 31.9 μ L, 0.30 *eq.*) and tetrabutylammonium acetate (691 mg, 2.29 mmol, 0.70 mL, 2.00 *eq.*) in *N*-methyl pyrrolidone (10 mL) was degassed with nitrogen then stirred at 100 °C for 12 hours. After such time the reaction mixture was diluted with water (100 mL), extracted with ethyl acetate (60 mL $\times$ 3) and the combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 10-20%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-ethyl-benzonitrile (310 mg, 0.44 mmol, 39% yield) as a yellow solid. LCMS $[M+1]^+ = 290.1$; ¹H NMR (400 Hz, DMSO-*d*₆) δ = 7.83 - 7.78 (m, 1H), 7.73 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.50 - 7.47 (m, 1H), 3.71 (s, 3H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H).

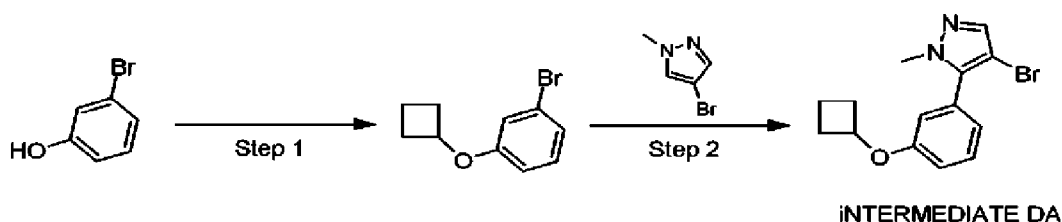
[0259] The INTERMEDIATES D-1 to D-20 shown in Table I-V were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE CJ.

Table I-V		
Intermediate	Structure	Spectral Data
D-1		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethylbenzonitrile LCMS $[M+1]^+ = 289.9$; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.67 (d, <i>J</i> = 1.2 Hz, 1H), 7.60 - 7.55 (m, 2H), 7.38 (d, <i>J</i> = 8.0 Hz, 1H), 5.30 (s, 1H), 3.80 (s, 3H), 2.79 (q, <i>J</i> = 7.6 Hz, 2H), 1.33 (t, <i>J</i> = 7.6 Hz, 3H)
D-2I		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-ethylbenzonitrile LCMS $[M+1]^+ = 290.0$; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.67 (d, <i>J</i> = 8.0 Hz, 1H), 7.49 (s, 1H), 7.36 (dd, <i>J</i> = 2.0, 8.0 Hz, 1H), 7.22 (d, <i>J</i> = 1.2 Hz, 1H), 3.72 (s, 3H), 2.72 (q, <i>J</i> = 7.6 Hz, 2H), 1.23 (t, <i>J</i> = 7.6 Hz, 3H)
D-3		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-cyclopropylbenzonitrile LCMS $[M+1]^+ = 304.1$; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.51 (d, <i>J</i> = 2.0 Hz, 1H), 7.43 - 7.39 (m, 1H), 7.36 - 7.31 (m, 1H), 3.79 (s, 3H), 2.01 (tt, <i>J</i> = 5.2, 8.4 Hz, 1H), 1.18 - 1.11 (m, 2H), 0.86 - 0.78 (m, 2H)
D-4		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-5-methylbenzonitrile LCMS $[M+1]^+ = 312.0$; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.71 (s, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 3.81 (s, 3H), 2.51 (s, 3H)
D-5		3-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-naphthonitrile LCMS $[M+1]^+ = 312.1$; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.43 (s, 1H), 8.04 - 7.96 (m, 2H), 7.95 (s, 1H), 7.79 - 7.70 (m, 2H), 7.64 (s, 1H), 3.85 (s, 3H)

D-6		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4,5-dimethoxybenzonitrile LCMS [M+] ⁺ = 324.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.59 (s, 1H), 7.23 (s, 1H), 6.87 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.83 (s, 3H)
D-7		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-4-methoxybenzonitrile LCMS [M+] ⁺ = 327.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.83 (s, 1H), 7.61 (s, 1H), 6.96 (s, 1H), 4.01 (s, 3H), 3.84 (s, 3H)
D-8		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4,5-dimethylbenzonitrile LCMS [M+] ⁺ = 292.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.60 (s, 1H), 7.58 (s, 1H), 7.22 (s, 1H), 3.79 (s, 3H), 2.40 (s, 3H), 2.39 (s, 3H)
D-9		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-4-methylbenzonitrile LCMS [M+] ⁺ = 312.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.82 (s, 1H), 7.59 (s, 1H), 7.34 (s, 1H), 3.81 (s, 3H), 2.53 (s, 3H)
D-10		4-bromo-5-(4-isopropylphenyl)-1-methyl-1H-pyrazole LCMS [M+] ⁺ = 281.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.39 - 7.32 (m, 4H), 3.83 (s, 3H), 1.31 (d, J = 6.8 Hz, 6H)
D-11		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-5-methoxybenzonitrile LCMS [M+] ⁺ = 328.0; ¹ H NMR (400 MHz, MeOD) δ = 7.67 (s, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 4.03 (s, 3H), 3.77 (s, 3H)
D-12		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethoxyterephthalonitrile LCMS [M+] ⁺ = 306.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.53 (d, J = 2.0 Hz, 1H), 7.49 (dd, J = 2.4, 8.8 Hz, 1H), 7.44 (s, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.73 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H)
D-13		6-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2,3-dichlorobenzonitrile LCMS [M+] ⁺ = 392.3; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.83 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H)
D-14		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-chloro-4-methylbenzonitrile LCMS [M+] ⁺ = 311.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.83 (s, 1H), 7.61 (s, 1H), 6.96 (s, 1H), 4.01 (s, 3H), 3.84 (s, 3H)
D-15		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-chloro-5-methylbenzonitrile LCMS [M+] ⁺ = 312; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.62 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.31 - 7.26 (m, 1H), 3.81 (d, J = 1.2 Hz, 3H), 2.54 (s, 3H)

D-16		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-cyclopropylbenzonitrile LCMS [M+1] ⁺ = 304.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.71 (d, <i>J</i> = 8.4 Hz, 1H), 7.59 (s, 1H), 7.26 - 7.23 (dd, <i>J</i> = 1.6, 8.4, 1H), 7.11 (d, <i>J</i> = 1.6 Hz, 1H), 3.81 (s, 3H), 2.03 - 1.99 (m, 1H), 1.20 - 1.17 (m, 2H), 0.87 - 0.82 (m, 2H)
D-17		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4,5-dichlorobenzonitrile LCMS [M+1] ⁺ = 329.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.93 (s, 1H), 7.60 (m, 2H), 3.83 (s, 3H)
D-18		6-(4-bromo-1-methyl-1H-pyrazol-5-yl)-3-chloro-2-methylbenzonitrile LCMS [M+1] ⁺ = 312.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.71 (d, <i>J</i> = 8.4 Hz, 1H), 7.59 (s, 1H), 7.24 (d, <i>J</i> = 8.4 Hz, 1H), 3.79 (s, 3H), 2.71 (s, 3H)
D-19		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-methylbenzonitrile LCMS [M+1] ⁺ = 312.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.59 (s, 1H), 7.48 (d, <i>J</i> = 1.2 Hz, 1H), 7.29 (d, <i>J</i> = 1.6 Hz, 1H), 3.81 (s, 3H)
D-20		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-propylbenzonitrile LCMS [M+1] ⁺ = 305.9; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.84 - 7.77 (m, 1H), 7.74 (s, 1H), 7.66 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (d, <i>J</i> = 7.6 Hz, 1H), 3.71 (s, 3H), 2.89 - 2.83 (m, 2H), 1.75 - 1.64 (m, 2H), 0.98 - 0.92 (m, 3H)

INTERMEDIATE DA



[0260] **Step 1:** A mixture of 3-bromophenol (1.00 g, 5.78 mmol, 1.00 *eq.*), bromocyclobutane (1.17 g, 8.65 mmol, 0.82 mL, 1.50 *eq.*) and potassium carbonate (3.20 g, 23.1 mmol, 4.00 *eq.*) in DMF (10 mL) and stirred at 120°C for 6 hours. The reaction mixture was diluted with water (80 mL) and extracted with (petroleum ether/ethyl acetate 20%) (50 mL × 3) and the combined extracts were washed with aqueous sodium hydroxide (1.00 M, 50 mL), brine (50 mL) and dried over sodium sulfate and concentrated to give 1-bromo-3-(cyclobutoxy)benzene (1.20 g, 5.27 mmol, 91% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.04 - 6.93 (m, 2H), 6.86 (t, *J* = 2.4 Hz, 1H), 6.64 (ddd, *J* = 1.2, 2.4, 8.0 Hz, 1H),

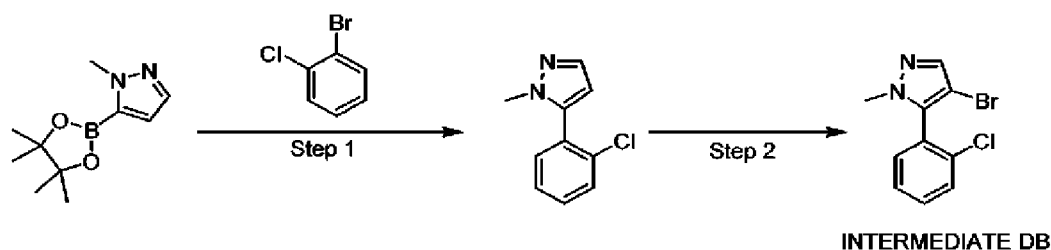
4.60 - 4.44 (m, 1H), 2.34 (td, $J = 2.8, 6.8, 8.0, 9.6$ Hz, 2H), 2.14 - 1.98 (m, 2H), 1.83 - 1.71 (m, 1H), 1.66 - 1.50 (m, 1H).

[0261] **Step 2:** 1-bromo-3-(cyclobutoxy)benzene (300 mg, 1.32 mmol, 1.00 *eq.*), 4-bromo-1-methyl-pyrazole (213 mg, 1.32 mmol, 1.00 *eq.*), palladium acetate (2.97 mg, 13.2 μ mol, 0.01 *eq.*), tetrabutylammonium acetate (224 mg, 2.91 mmol, 2.20 *eq.*), 2-methylpropanoic acid (34.9 mg, 396 μ mol, 36.8 μ L, 0.30 *eq.*) and DavePhos (10.4 mg, 26.4 μ mol, 0.02 *eq.*) in NMP (5 mL) was degassed with nitrogen and heated to 100°C for 12 hours. The reaction mixture was then diluted with water (20 mL), extracted with ethyl acetate (30 mL $\times$ 3) and the combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 1-5%) to give 4-bromo-5-[3-(cyclobutoxy)phenyl]-1-methyl-pyrazole (40.0 mg) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.54 (s, 1H), 7.45 (s, 1H), 6.98 - 6.90 (m, 2H), 6.86 - 6.83 (m, 1H), 4.68 (t, $J = 7.2$ Hz, 1H), 3.83 (s, 3H), 2.54 - 2.40 (m, 2H), 2.27 - 2.14 (m, 2H), 1.95 - 1.66 (m, 2H).

[0262] The INTERMEDIATES E-1 and E-2 shown in Table I-VI were prepared following the teachings of the General Reaction Schemes and the method to prepare Intermediate DA.

Table I-VI		
Intermediate	Structure	Spectral Data
E-1		4-bromo-5-(4-cyclobutoxyphenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 307.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.52 (s, 1H), 7.30 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 4.70 (quin, $J = 7.2$ Hz, 1H), 3.81 (s, 3H), 2.54 - 2.47 (m, 2H), 2.28 - 2.19 (m, 2H), 1.94 - 1.87 (m, 1H), 1.78 - 1.72 (m, 1H)
E-2		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethoxybenzonitrile LCMS [M+1] ⁺ = 307.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.36 (d, $J = 8.8$ Hz, 1H), 7.30 (d, $J = 2.8$ Hz, 1H), 7.26 - 7.21 (dd, $J = 2.8, 8.8$ Hz, 1H), 4.16 - 4.10 (q, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 1.49 (t, $J = 7.2$ Hz, 3H)

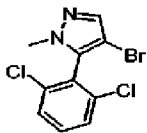
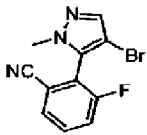
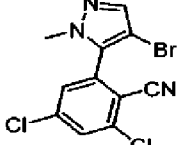
INTERMEDIATE DB



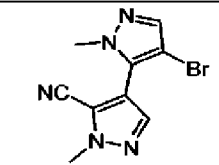
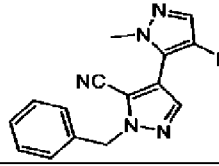
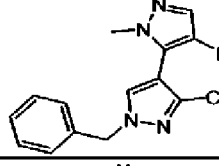
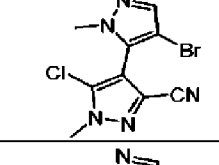
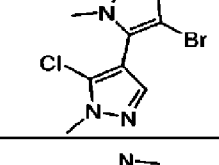
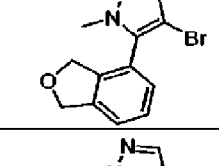
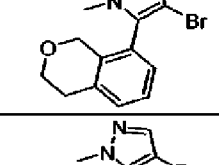
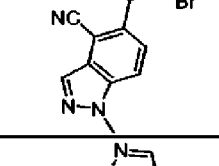
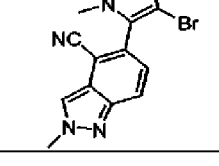
[0263] **Step 1:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.50 g, 7.21 mmol, 1.00 *eq.*), 1-bromo-2-chloro-benzene (1.38 g, 7.21 mmol, 0.84 mL, 1.00 *eq.*), sodium carbonate (2.29 g, 21.6 mmol, 3.00 *eq.*), Pd(dppf)Cl₂ (528 mg, 0.72 mmol, 0.10 *eq.*) in water (2.4 mL) and dioxane (12 mL) was degassed with nitrogen then stirred at 80 °C for 2 hours. After such time the mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate 10-20%) to give 5-(2-chlorophenyl)-1-methyl-pyrazole (0.56 g, 2.88 mmol, 40% yield) as a yellow solid. LCMS [M+1]⁺ = 193.1; ¹H NMR (400 MHz, CDCl₃) δ = 7.56 (d, *J* = 2.0 Hz, 1H), 7.52 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.43 - 7.33 (m, 3H), 6.30 (d, *J* = 2.0 Hz, 1H), 3.74 (s, 3H).

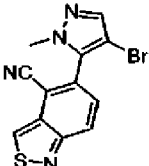
[0264] **Step 2:** A mixture of 5-(2-chlorophenyl)-1-methyl-pyrazole (200 mg, 1.04 mmol, 1.00 *eq.*), *N*-bromo-succinimide (203 mg, 1.14 mmol, 1.10 *eq.*) in acetonitrile (2 mL) was degassed with nitrogen then stirred at 0 °C for 2 hours. After such time the mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (Petroleum ether/ethyl acetate 20%) to give 4-bromo-5-(2-chlorophenyl)-1-methyl-pyrazole (220 mg, 0.77 mmol, 74% yield) as a yellow solid. LCMS [M+1]⁺ = 273.1; ¹H NMR (400 MHz, CDCl₃) δ = 7.59 - 7.55 (m, 2H), 7.50 - 7.40 (m, 2H), 7.36 - 7.33 (m, 1H), 3.74 (s, 3H).

[0265] The INTERMEDIATES F-1 to F-22 shown in Table I-VII were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE DB.

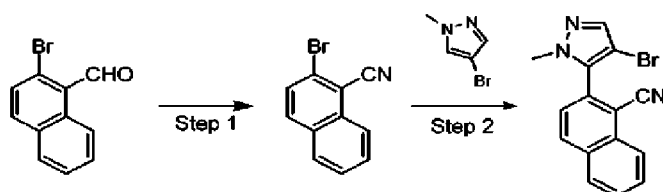
Table I-VII		
Intermediate	Structure	Spectral Data
F-1		4-bromo-5-(2,6-dichlorophenyl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 306.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.59 (s, 1H), 7.53-7.51 (m, 1H), 7.50-7.47 (m, 1H), 7.46-7.35 (m, 1H), 3.70 (s, 3H)
F-2		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-3-fluorobenzonitrile LCMS [M+1] ⁺ = 282.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.72 - 7.64 (m, 2H), 7.63 (s, 1H), 7.55 - 7.49 (m, 1H), 3.80 (s, 3H)
F-3		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4,6-dichlorobenzonitrile LCMS [M+1] ⁺ = 331.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.70 (d, <i>J</i> = 2.0 Hz, 1H), 7.61 (s, 1H), 7.39 (d, <i>J</i> = 2.0 Hz, 1H), 3.84 (s, 3H)

F-4		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-methoxybenzonitrile LCMS [M+] ⁺ = 327.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.57 (s, 1H), 7.11 (d, <i>J</i> = 2.0 Hz, 1H), 7.03 (d, <i>J</i> = 2.0 Hz, 1H), 4.02 (s, 3H), 3.82 (s, 3H)
F-5		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methoxy-6-chlorobenzonitrile LCMS [M+] ⁺ = 328.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 7.75 (s, 1H), 7.56 (d, <i>J</i> = 2.4 Hz, 1H), 7.28 (d, <i>J</i> = 2.4 Hz, 1H), 3.93 (s, 3H), 3.75 (s, 3H)
F-6		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methoxy-6-chlorobenzonitrile LCMS [M+] ⁺ = 328.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.27 (d, <i>J</i> = 8.8 Hz, 1H), 4.03 (s, 3H), 3.80 (s, 3H)
F-7		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methoxy-6-methylbenzonitrile LCMS [M+] ⁺ = 308.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.58 (s, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 7.27 (d, <i>J</i> = 8.8 Hz, 1H), 4.03 (s, 3H), 3.80 (s, 3H), 2.50 (s, 3H)
F-8		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)quinoline LCMS [M+] ⁺ = 290.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.21 (d, <i>J</i> = 8.8 Hz, 1H), 8.07 (d, <i>J</i> = 8.4 Hz, 1H), 7.81 (d, <i>J</i> = 8.8 Hz, 2H), 7.70 (dt, <i>J</i> = 1.2, 7.6 Hz, 1H), 7.58 - 7.51 (m, 1H), 7.50 (s, 1H), 4.08 (s, 3H)
F-9		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methoxy-1-naphthonitrile LCMS [M+] ⁺ = 344.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 8.40 (d, <i>J</i> = 8.0 Hz, 1H), 8.29 (d, <i>J</i> = 8.0 Hz, 1H), 7.79 (ddd, <i>J</i> = 1.2, 7.2, 8.4 Hz, 1H), 7.70 (ddd, <i>J</i> = 1.2, 7.2, 8.4 Hz, 1H), 7.64 (s, 1H), 6.80 (s, 1H), 4.12 (s, 3H), 3.88 (s, 3H)
F-10		6-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-ethyl-3-methoxybenzonitrile LCMS [M+] ⁺ = 322.1; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.56 (s, 1H), 7.26 - 7.22 (m, 1H), 7.18 - 7.11 (m, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 2.96 (q, <i>J</i> = 7.6 Hz, 2H), 1.28 - 1.24 (m, 3H)
F-11		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-3-chloro-1-naphthonitrile LCMS [M+] ⁺ = 346.0, 348.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.78 (s, 1H), 8.23 (t, <i>J</i> = 9.2, 2H), 7.95 - 7.90 (m, 2H), 7.85 (s, 1H), 3.74 (s, 1H)
F-12		1'-benzyl-4-bromo-5'-chloro-2-methyl-1H,2H-3,4'-bipyrazole LCMS [M+] ⁺ = 353.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.67 (s, 1H), 7.54 (s, 1H), 7.41 - 7.33 (m, 3H), 7.31 - 7.27 (m, 2H), 5.43 (s, 2H), 3.79 (s, 3H)

F-13		4-bromo-1',2-dimethyl-1'H,2H-[3,4'-bipyrazole]-5'-carbonitrile LCMS [M+1] ⁺ = 265.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.70 (s, 1H), 7.56 (s, 1H), 4.16 (s, 3H), 3.87 (s, 3H)
F-14		1'-benzyl-4-bromo-2-methyl-1'H,2H-[3,4'-bipyrazole]-5'-carbonitrile LCMS [M+1] ⁺ = 342.0
F-15		1'-benzyl-4-bromo-2-methyl-1'H,2H-[3,4'-bipyrazole]-3'-carbonitrile LCMS [M+1] ⁺ = 342.0; ¹ H NMR (400 MHz, CDCl ₃ -d) δ = 7.61 (s, 1H), 7.54 (s, 1H), 7.47 - 7.39 (m, 1H), 7.36 - 7.30 (m, 2H), 5.43 (s, 2H), 3.87 (s, 3H)
F-16		4-bromo-5'-chloro-1',2-dimethyl-1'H,2H-[3,4'-bipyrazole]-3'-carbonitrile LCMS [M+1] ⁺ = 302.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.59 (s, 1H), 4.04 (s, 3H), 3.84 (s, 3H)
F-17		4-bromo-5'-chloro-1',2-dimethyl-1'H,2H-3,4'-bipyrazole LCMS [M+1] ⁺ = 277.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.60 (s, 1H), 7.53 (s, 1H), 3.94 (s, 3H), 3.79 (s, 3H)
F-18		4-bromo-5-(1,3-dihydroisobenzofuran-4-yl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 280.9; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.45 - 7.35 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 5.26 - 5.11 (m, 3H), 4.88 - 4.83 (m, 1H), 3.72 (s, 3H)
F-19		4-bromo-5-(isochroman-8-yl)-1-methyl-1H-pyrazole LCMS [M+1] ⁺ = 293.0; ¹ H NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.34 - 7.26 (m, 2H), 7.04 (d, J = 6.8 Hz, 1H), 4.65 - 4.57 (m, 1H), 4.34 - 4.28 (m, 1H), 4.07 - 3.92 (m, 2H), 3.65 (s, 3H), 3.05 - 2.88 (m, 2H)
F-20		5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-1-methyl-1H-indazole-4-carbonitrile LCMS [M+1] ⁺ = 318.0
F-21		5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-methyl-2H-indazole-4-carbonitrile LCMS [M+1] ⁺ = 318.0

F-22		5-(4-bromo-1-methyl-1H-pyrazol-5-yl)benzo[c]isothiazole-4-carbonitrile LCMS $[M+1]^+ = 318.9$; ^1H NMR (400 MHz, CDCl_3) $\delta = 9.62$ (d, $J = 0.8$ Hz, 1H), 8.22 (dd, $J = 1.2, 9.2$ Hz, 1H), 7.65 (s, 1H), 7.50 (d, $J = 9.2$ Hz, 1H), 3.88 (s, 3H)

INTERMEDIATE DC



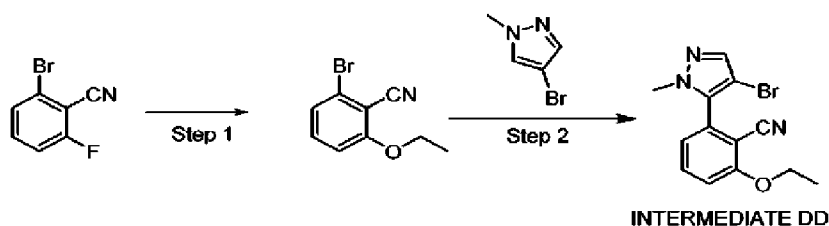
INTERMEDIATE DC

[0266] **Step 1:** To a solution of 2-bromonaphthalene-1-carbaldehyde (220 mg, 0.94 mmol, 1.00 *eq.*) in water (5 mL) was added amino hydrogen sulfate (212 mg, 1.87 mmol, 2.00 *eq.*). The mixture was stirred at 50 °C for 12 hours. The suspension was then filtered and the filter cake dried under reduced pressure to give (1*E*)-2-bromonaphthalene-1-carbaldehyde oxime (220 mg, 0.88 mmol, 94% yield) as a white solid which used without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 11.79$ (s, 1H), 8.58 (s, 1H), 8.55 (dd, $J = 1.6, 8.0$ Hz, 1H), 8.03 - 7.98 (m, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 1H), 7.67 - 7.57 (m, 2H). To a solution of (1*E*)-2-bromonaphthalene-1-carbaldehyde oxime (220 mg, crude) in THF (5 mL) was added triethylamine (890 mg, 8.80 mmol, 1.22 mL) and trifluoroacetic anhydride (924 mg, 4.40 mmol, 0.61 mL) and the mixture stirred at 20 °C for 1 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (SiO_2 , petroleum ether/ethyl acetate 10%) to give 2-bromonaphthalene-1-carbonitrile (190 mg, 0.82 mmol, 93% yield) as a white solid. GCMS $[M+1]^+ = 230.9$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 8.26$ (d, $J = 8.8$ Hz, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 1H), 7.85 (dt, $J = 1.2, 8.4$ Hz, 1H), 7.79 - 7.71 (m, 1H).

[0267] **Step 2:** A mixture of 2-bromonaphthalene-1-carbonitrile (190 mg, 0.82 mmol, 1.00 *eq.*), 4-bromo-1-methyl-pyrazole (132 mg, 0.82 mmol, 1.00 *eq.*), tetrabutylammonium acetate (494 mg, 1.64 mmol, 0.50 mL, 2.00 *eq.*), DavePhos (6.4 mg, 16 μmol , 0.02 *eq.*), 2-methylpropanoic acid (22 mg, 246 μmol , 23 μL , 0.30 *eq.*) and palladium acetate (1.8 mg, 8.2 μmol , 0.01 *eq.*) in *N*-methyl pyrrolidone (NMP) (6 mL) was degassed with nitrogen then the

mixture was stirred at 100 °C for 12 hours. After such time the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (0.1% formic acid condition) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (190 mg, 0.61 mmol, 74% yield) as a yellow oil. LCMS $[M+1]^+ = 314.1$; ^1H NMR (400 MHz, DMSO- d_6) δ = 8.49 (d, J = 8.4 Hz, 1H), 8.24 (t, J = 8.4 Hz, 2H), 7.92 (dt, J = 1.2, 8.4 Hz, 1H), 7.87 - 7.82 (m, 1H), 7.81 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 3.79 (s, 3H).

INTERMEDIATE DD

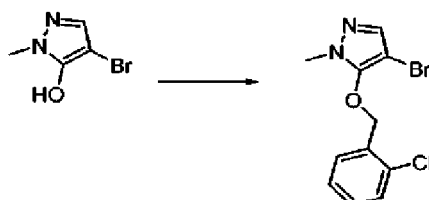


[0268] **Step 1:** To a solution of ethyl alcohol (207 mg, 4.50 mmol, 0.26 mL, 3.00 *eq.*) in THF (3 mL) was added sodium hydride (180 mg, 4.50 mmol, 60.0% purity, 3.00 *eq.*), followed by a solution of 2-bromo-6-fluorobenzonitrile (300 mg, 1.50 mmol, 1.00 *eq.*) in THF (1 mL) in a dropwise fashion. After the addition was complete the mixture was stirred at 25 °C for 3 hours. After such time the reaction was quenched with water (0.2 mL) and concentrated in vacuum and the residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 10%) to give 2-bromo-6-ethoxybenzonitrile (200 mg, 0.89 mmol, 59% yield) as a white solid. ^1H NMR (400 MHz, CDCl₃) δ = 7.38 - 7.32 (t, J = 8.4 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H).

[0269] **Step 2:** A mixture of 2-bromo-6-ethoxybenzonitrile (200 mg, 0.89 mmol, 1.00 *eq.*), 4-bromo-1-methylpyrazole (185 mg, 1.15 mmol, 1.30 *eq.*), palladium acetate (2.0 mg, 8.9 μmol , 0.01 *eq.*), DavePhos (7.0 mg, 17.7 μmol , 0.02 *eq.*), 2-methylpropanoic acid (23.4 mg, 265 μmol , 25 μL , 0.30 *eq.*) and tetrabutylammonium acetate (533 mg, 1.77 mmol, 2.00 *eq.*) was degassed with nitrogen then the mixture was stirred at 100 °C for 15 hours. After such time the mixture was diluted with ethyl acetate (20 mL), washed with water (20 mL × 3) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was then purified by prep-TLC (SiO₂, petroleum

ether/ethyl acetate 20%) to give 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-ethoxybenzonitrile (60.0 mg, 0.20 mmol, 22% yield) as a white solid. LCMS $[M+1]^+ = 306.1$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.56$ (dd, $J = 7.6, 8.4$ Hz, 1H), 7.49 (s, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 1.46 (t, $J = 7.2$ Hz, 3H).

INTERMEDIATE DE



INTERMEDIATE DE

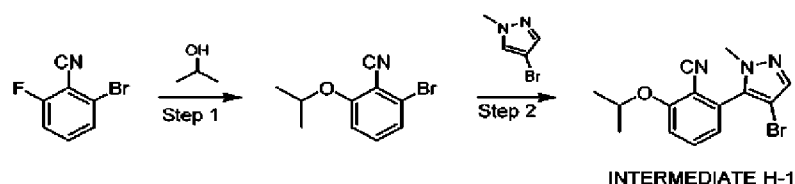
[0270] A mixture of 4-bromo-2-methyl-pyrazol-3-ol (300 mg, 1.69 mmol, 1.00 *eq.*), 1-(bromomethyl)-2-chloro-benzene (348 mg, 1.69 mmol, 0.22 mL, 1.00 *eq.*), and potassium carbonate (469 mg, 3.39 mmol, 2.00 *eq.*) in DMF (8 mL) was stirred at 18 °C for 2 hours. After such time the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and the residue purified by reversed-phase HPLC (0.1% FA condition) to give 4-bromo-5-[(2-chlorophenyl)methoxy]-1-methyl-pyrazole (220 mg, 0.72 mmol, 42% yield) as a yellow solid. LCMS $[M+1]^+ = 303.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.48 - 7.43$ (m, 2H), 7.37 - 7.27 (m, 3H), 5.40 (s, 2H), 3.55 (s, 3H).

[0271] The INTERMEDIATES to G-1 to G-4 shown in Table I-VIII were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE DE.

Table I-VIII		
Intermediate	Structure	Spectral Data
G-1		4-bromo-5-((3-chlorobenzyl)oxy)-1-methyl-1H-pyrazole LCMS $[M+1]^+ = 303.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.43$ (d, $J = 1.6$ Hz, 1H), 7.37 - 7.35 (m, 1H), 7.34 - 7.30 (m, 2H), 7.28 (t, $J = 1.6$ Hz, 1H), 5.26 (s, 2H), 3.54 (s, 3H)
G-2		4-bromo-5-((4-chlorobenzyl)oxy)-1-methyl-1H-pyrazole LCMS $[M+1]^+ = 303.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.43 - 7.35$ (m, 2H), 7.35 - 7.29 (m, 3H), 5.25 (s, 2H), 3.49 (s, 3H)

G-3		4-bromo-5-((2-cyanobenzyl)oxy)-1-methyl-1H-pyrazole LCMS $[M+1]^+ = 294.1$; $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.75$ (d, $J = 7.6$ Hz, 1H), 7.69 - 7.59 (m, 2H), 7.55 - 7.49 (m, 1H), 7.32 (s, 1H), 5.46 (s, 2H), 3.64 (s, 3H)
G-4		2-(((4-bromo-1-methyl-1H-pyrazol-5-yl)oxy)methyl)-3-chlorobenzonitrile LCMS $[M+1]^+ = 327.9$; $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.63$ - 7.58 (m, 1H), 7.58 - 7.54 (m, 2H), 7.34 - 7.30 (m, 1H), 5.46 (s, 2H), 3.68 (s, 3H)

INTERMEDIATE H-1



[0272] **Step 1:** A mixture of 2-bromo-6-fluorobenzonitrile (600 mg, 3.00 mmol, 1.00 *eq.*), propan-2-ol (225 mg, 3.75 mmol, 0.29 mL, 1.25 *eq.*), cesium carbonate (1.47 g, 4.50 mmol, 1.50 *eq.*) in DMF (6 mL) was stirred at 75 °C for 1 hour. After such time the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (0.1% formic acid condition) to give 2-bromo-6-isopropoxy-benzonitrile (540 mg, 2.25 mmol, 75% yield) as a white solid. LCMS $[M+1]^+ = 241.9$; $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) $\delta = 7.56$ (t, $J = 8.4$ Hz, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 4.90 - 4.75 (m, 1H), 1.32 (d, $J = 6.0$ Hz, 6H).

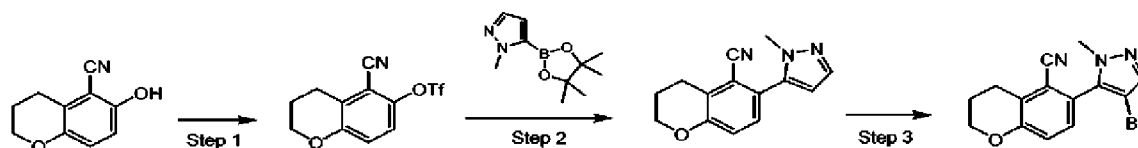
[0273] **Step 2:** A mixture of 2-bromo-6-isopropoxy-benzonitrile (500 mg, 2.08 mmol, 1.00 *eq.*), 4-bromo-1-methyl-pyrazole (335 mg, 2.08 mmol, 1.00 *eq.*), diacetoxypalladium (4.7 mg, 0.021 mmol, 0.01 *eq.*), DavePhos (16 mg, 0.042 mmol, 0.02 *eq.*), tetrabutylammonium;acetate (1.26 g, 4.16 mmol, 2.00 *eq.*) and 2-methylpropanoic acid (55 mg, 0.63 mmol, 0.06 mL, 0.30 *eq.*) in 1-methyl-2-pyrrolidinone (7 mL) was degassed with nitrogen then stirred at 100 °C for 12 hours. After such time the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (40 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (0.1% formic acid condition) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-isopropoxy-benzonitrile (160 mg, 0.50 mmol, 24 yield) as a

white solid. LCMS $[M+1]^+ = 319.9$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 7.81 - 7.76$ (m, 1H), 7.72 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.14 (d, $J = 7.2$ Hz, 1H), 4.88 (td, $J = 6.0, 12.0$ Hz, 1H), 3.71 (s, 3H), 1.36 (d, $J = 6.0$ Hz, 6H).

[0274] The INTERMEDIATES to H-2 to H-8 shown in Table I-IX were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE H-1.

Table I-IX		
Intermediate	Structure	Spectral Data
H-2		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxybenzonitrile LCMS $[M+1]^+ = 318.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.71 - 7.64$ (m, 1H), 7.58 (s, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.05 - 7.01 (m, 1H), 3.92 (td, $J = 2.8, 5.6$ Hz, 1H), 0.96 - 0.91 (m, 4H)
H-3		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-cyclobutoxybenzonitrile LCMS $[M+1]^+ = 334.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.65 - 7.59$ (m, 1H), 7.59 (s, 1H), 7.00 - 6.93 (m, 2H), 4.80 (q, $J = 7.2$ Hz, 1H), 3.82 - 3.79 (s, 3H), 2.61 - 2.48 (m, 2H), 2.39 - 2.27 (m, 2H), 2.03 - 1.91 (m, 1H), 1.84 - 1.70 (m, 1H)
H-4		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-propoxybenzonitrile LCMS $[M+1]^+ = 320.0$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 7.80$ (dd, $J = 8.0, 8.4$ Hz, 1H), 7.73 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.17 (d, $J = 7.6$ Hz, 1H), 4.18 (dt, $J = 2.0, 6.4$ Hz, 2H), 1.81 (q, $J = 7.6$ Hz, 2H), 1.02 (t, $J = 7.6$ Hz, 3H)
H-5		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxybenzonitrile LCMS $[M+1]^+ = 353.9$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.57$ (s, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.04 (d, $J = 2.0$ Hz, 1H), 3.95 - 3.90 (m, 1H), 3.81 (s, 3H), 0.99 - 0.94 (m, 4H)
H-6		6-(4-bromo-1-methyl-1H-pyrazol-5-yl)-3-chloro-2-cyclopropoxybenzonitrile LCMS $[M+1]^+ = 354.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.73$ (d, $J = 8.4$ Hz, 1H), 7.60 (s, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 4.61 (m, 1H), 3.82 (s, 3H), 1.11 - 1.04 (m, 2H), 0.80 - 0.72 (m, 2H)
H-7		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-(trifluoromethyl)benzonitrile ^1H NMR (500 MHz, CDCl_3) $\delta = 7.69$ (d, $J = 1.2$ Hz, 1H), 7.59 (s, 1H), 7.29 (d, $J = 1.2$ Hz, 1H), 4.01 - 3.97 (m, 1H), 3.81 (s, 3H), 1.01 - 0.97 (m, 4H)
H-8		3-(4-bromo-1-methyl-1H-pyrazol-5-yl)-1-cyclopropoxy-2-naphthonitrile ^1H NMR (400 MHz, CDCl_3) $\delta = 8.26$ (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.76 - 7.70 (m, 1H), 7.70 - 7.65 (m, 1H), 7.63 (s, 1H), 7.57 (s, 1H), 4.74 (tt, $J = 2.8, 6.0$ Hz, 1H), 3.86 (s, 3H), 1.13 - 1.07 (m, 2H), 0.95 - 0.87 (m, 2H)

INTERMEDIATE I-1



[0275] **Step 1:** To a solution of 6-hydroxychromane-5-carbonitrile (150 mg, 0.86 mmol, 1.00 *eq.*) and triethylamine (2.57 mmol, 0.36 mL, 3.00 *eq.*) in dichloromethane (2 mL) was added a solution of trifluoromethanesulfonic anhydride (0.86 mmol, 0.141 mL, 1.00 *eq.*) in dichloromethane (1 mL) dropwise at 0 °C. The mixture was then stirred at 0 °C for 0.5 hour. After such time the mixture was diluted with ethyl acetate (50 mL), washed with brine (50 mL $\times$ 3) and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether/ ethyl acetate 10%) to give (5-cyanochroman-6-yl) trifluoromethanesulfonate (80 mg, 0.26 mmol, 30% yield) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ = 7.21 - 7.15 (m, 1H), 7.09 - 7.04 (m, 1H), 4.31 - 4.20 (m, 2H), 3.00 (t, *J* = 6.4 Hz, 2H), 2.18 - 2.02 (m, 2H).

[0276] **Step 2:** A mixture of (5-cyanochroman-6-yl) trifluoromethanesulfonate (70 mg, 0.23 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (71 mg, 0.34 mmol, 1.50 *eq.*), Pd(dtbpf)Cl₂ (15 mg, 0.23 mmol, 0.10 *eq.*), sodium bicarbonate (38 mg, 0.46 mmol, 2.00 *eq.*) in DMF (2 mL) was degassed with nitrogen. The mixture was then stirred at 80 °C for 1 hour, cooled to 25 °C, diluted with ethyl acetate (30 mL) and washed with brine (30 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ ethyl acetate 30%) to give 6-(2-methylpyrazol-3-yl)chromane-5-carbonitrile (40 mg, 0.17 mmol, 73% yield) as a white solid. LCMS [M+1]⁺ = 240.0; ¹H NMR (400 MHz, CDCl₃) = 7.57 (d, *J* = 1.6 Hz, 1H), 7.19 - 7.14 (m, 1H), 7.12 - 7.06 (m, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 4.30 - 4.24 (m, 2H), 3.82 (s, 3H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.17 - 2.09 (m, 2H).

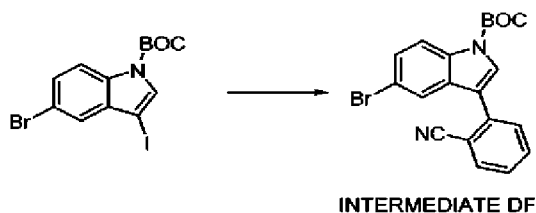
[0277] **Step 3:** To a solution of 6-(2-methylpyrazol-3-yl)chromane-5-carbonitrile (30 mg, 0.125 mmol, 1.00 *eq.*) in acetonitrile (1.5 mL) was added NBS (34 mg, 0.19 mmol, 1.50 *eq.*). The mixture was stirred at 25 °C for 1 hour then concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether/ ethyl acetate 30%) to give 6-(4-bromo-2-methylpyrazol-3-yl)chromane-5-carbonitrile (25 mg, 0.079 mmol, 63% yield) as a yellow solid. LCMS [M+1]⁺

= 320.1; ^1H NMR (400 MHz, CDCl_3) δ = 7.57 (s, 1H), 7.18 - 7.11 (m, 2H), 4.29 (dd, J = 4.4, 6.0 Hz, 2H), 3.79 (s, 3H), 3.05 (dt, J = 2.0, 6.4 Hz, 2H), 2.15 (dq, J = 4.4, 6.4 Hz, 2H).

[0278] The INTERMEDIATES to I-2 to I-4 shown in Table I-X were prepared following the teachings of the General Reaction Schemes and the method to prepare INTERMEDIATE I-1

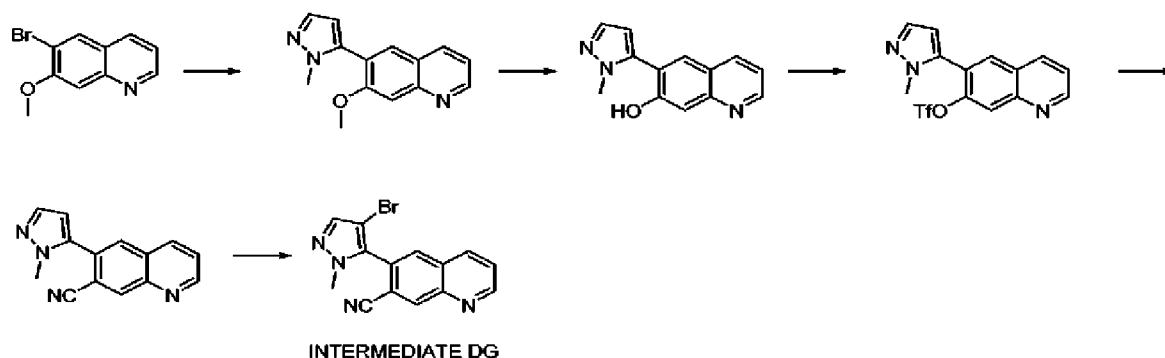
Table I-X		
Intermediate	Structure	Spectral Data
I-2		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-fluoro-1-naphthonitrile LCMS $[M+1] = 329.9$; ^1H NMR (400 MHz, CDCl_3) δ = 8.49 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.75 (dt, J = 5.2, 8.0 Hz, 1H), 7.66 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 7.2, 9.2 Hz, 1H), 3.86 (s, 3H)
I-3		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-7-fluoro-1-naphthonitrile LCMS $[M+1] = 329.9$; ^1H NMR (400 MHz, CDCl_3) δ = 8.21 (d, J = 8.4 Hz, 1H), 8.04 (dd, J = 5.4, 9.1 Hz, 1H), 8.00 (dd, J = 2.4, 9.5 Hz, 1H), 7.65 (s, 1H), 7.56 - 7.47 (m, 2H), 3.86 (s, 3H)
I-4		2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-8-fluoro-1-naphthonitrile ^1H NMR (400 MHz, CDCl_3) δ = 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.71 - 7.66 (m, 1H), 7.65 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.49 - 7.42 (m, 1H), 3.87 (s, 3H)

INTERMEDIATE DF



[0279] A mixture of *tert*-butyl 5-bromo-3-iodo-pyrrolo[2,3-*b*]pyridine-1-carboxylate (120 mg, 0.28 mmol, 1 *eq*), (2-cyanophenyl)boronic acid (83 mg, 0.57 mmol, 2 *eq*), $\text{Pd}(\text{dppf})\text{Cl}_2$ (21 mg, 0.03 mmol, 0.1 *eq*), NaHCO_3 (71 mg, 0.85 mmol) in DMF (2 mL) was degassed with nitrogen then stirred at 80 °C for 3 hr. After such time mixture was diluted with ethyl acetate (20 mL) and washed by water (20 mL x 3). The organic phase was concentrated and the residue purified by prep-TLC (SiO_2 , petroleum ether/ethyl acetate 15%) to give intermediate E-1, *tert*-butyl 5-bromo-3-(2-cyanophenyl)pyrrolo[2,3-*b*]pyridine-1-carboxylate (50 mg, 0.13 mmol, 44% yield) as a white solid. LCMS $[M-55]^+ = 342.1$; ^1H NMR (400 MHz, CDCl_3) δ = 8.62 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 8.03 (s, 1H), 7.84 (dd, J = 1.2, 8.0 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.52 (dt, J = 1.2, 7.6 Hz, 1H), 1.70 (s, 9H).

INTERMEDIATE DG



[0280] **Step 1:** A mixture of 6-bromo-7-methoxy-quinoline (100 mg, 0.420 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (105 mg, 0.504 mmol, 1.20 *eq.*), Pd(dtbpf)Cl₂ (27 mg, 0.042 mmol, 0.10 *eq.*) and sodium carbonate (89 mg, 0.840 mmol, 2.00 *eq.*) in dioxane (1.0 mL) and water (0.2 mL) was degassed with nitrogen. The mixture was then stirred at 80 °C for 2 hours, concentrated under reduced pressure and the residue purified by prep-TLC (SiO₂, ethyl acetate) to give 7-methoxy-6-(2-methylpyrazol-3-yl)quinoline (80 mg, 0.334 mmol, 80% yield) as a yellow solid. LCMS [M+1]⁺ = 240.2; ¹H NMR (400 MHz, CDCl₃) δ = 8.82 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.48 (s, 1H), 7.27 (dd, *J* = 4.4, 8.0 Hz, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H).

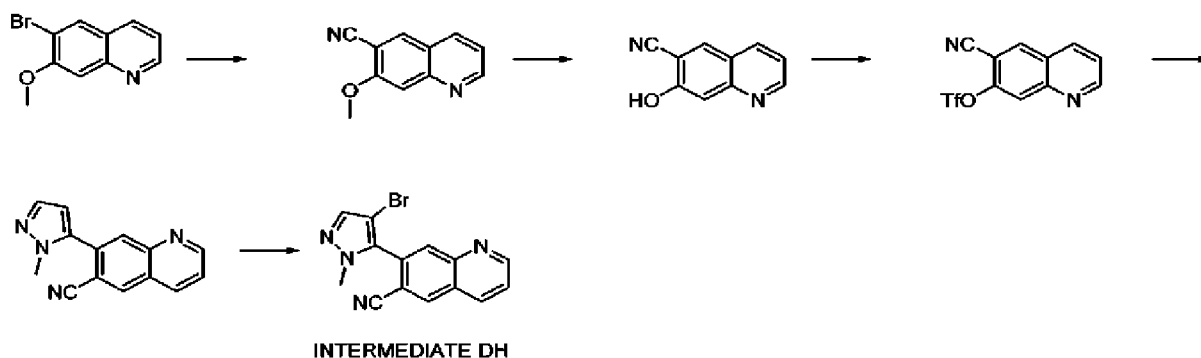
[0281] **Step 2:** A mixture of 7-methoxy-6-(2-methylpyrazol-3-yl)quinoline (500 mg, 2.09 mmol, 1.00 *eq.*) and pyridine hydrochloride (2.41 g, 20.9 mmol, 10.0 *eq.*) was stirred at 160 °C for 0.5 hour. After such time the residue was purified by reverse prep-HPLC (0.1% formic acid) to give 6-(2-methylpyrazol-3-yl)quinolin-7-ol (260 mg, 1.07 mmol, 51% yield, 92% purity) as a yellow solid. LCMS [M+1]⁺ = 226.1.

[0282] **Step 3:** To a solution of 6-(2-methylpyrazol-3-yl)quinolin-7-ol (260 mg, 1.15 mmol, 1.00 *eq.*) and triethylamine (0.32 mL, 2.31 mmol, 2.00 *eq.*) in dichloromethane (5 mL) was added trifluoromethanesulfonic anhydride (0.29 mL, 1.73 mmol, 1.50 *eq.*) in a dropwise fashion at 0 °C. The mixture was stirred at 20 °C for 1 hour, quenched with water (12 mL) and extracted with dichloromethane (15 mL × 3). The combined organic extracts were washed with brine (12 mL), dried over anhydrous sodium sulfate, filtered and concentrated and the residue purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 10-100%) to give [6-(2-methylpyrazol-3-yl)-7-quinolyl] trifluoromethanesulfonate (0.97 g, 0.706 mmol, 61%) as a yellow oil. LCMS [M+1]⁺ = 358.1.

[0283] **Step 4:** A mixture of [6-(2-methylpyrazol-3-yl)-7-quinolyl] trifluoromethanesulfonate (970 mg, 0.668 mmol, 1.00 eq.), zinc cyanide (157 mg, 1.34 mmol, 2.00 eq.), Pd₂(dba)₃ (61 mg, 0.67 mmol, 0.1 eq.), DPPF (74 mg, 0.134 mmol, 0.20 eq.) and zinc powder (4.3 mg, 0.67 mmol, 0.10 eq.) in DMF (10 mL) was degassed with nitrogen then stirred at 100 °C for 2 hours. After such time the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by HPLC (0.1% formic acid condition) to give 6-(2-methylpyrazol-3-yl)quinoline-7-carbonitrile (100 mg, 0.249 mmol, 37% yield) as a brown solid. LCMS [M+]⁺ = 235.2.

[0284] **Step 5:** To a solution of 6-(2-methylpyrazol-3-yl)quinoline-7-carbonitrile (90 mg, 0.384 mmol, 1.00 eq.) in acetonitrile (5 mL) was added *N*-bromosuccinimide (103 mg, 0.576 mmol, 1.50 eq.). The mixture was stirred at 20 °C for 0.5 hours then concentrated under reduced pressure and the residue was purified by prep-TLC (dichloromethane/methyl alcohol 10%) to give 6-(4-bromo-2-methyl-pyrazol-3-yl)quinoline-7-carbonitrile (50 mg, 0.160 mmol, 41% yield) as a yellow solid. LCMS [M+]⁺ = 315.1; ¹H NMR (400 MHz, CDCl₃) δ = 9.14 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.68 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.69 - 7.65 (m, 1H), 7.65 (s, 1H), 3.86 (s, 3H).

INTERMEDIATE DH



[0285] **Step1:** A mixture of 6-bromo-7-methoxy-quinoline (100 mg, 0.420 mmol, 1.00 eq.), zinc cyanide (98 mg, 0.840 mmol, 2.00 eq.), Pd₂(dba)₃ (38 mg, 0.042 mmol, 0.10 eq.), DPPF (47 mg, 0.084 mmol, 0.20 eq.) and zinc powder (2.8 mg, 0.042 mmol, 0.10 eq.) in DMF (2 mL) was degassed and purged with nitrogen. The mixture was then stirred at 100 °C for 2 hours then diluted with water (2 mL) and extracted with ethyl acetate (2 mL × 3). The

combined organic extracts were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by HPLC (0.1% formic acid) to give 7-methoxyquinoline-6-carbonitrile (56 mg, 0.304 mmol, 72% yield) as a white solid. LCMS $[M+1]^+ = 185.2$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.97$ (dd, $J = 1.6, 4.0$ Hz, 1H), 8.17 (s, 1H), 8.15 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.53 (s, 1H), 7.40 (dd, $J = 4.0, 8.4$ Hz, 1H), 4.09 (s, 3H).

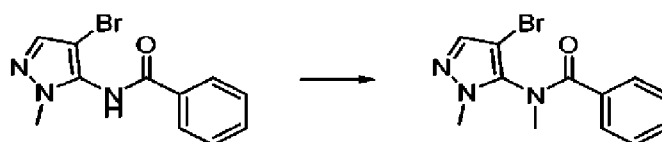
[0286] **Step 2:** To a solution of 7-methoxyquinoline-6-carbonitrile (1.40 g, 7.60 mmol, 1.00 eq) in toluene (20 mL) was added aluminum trichloride (3.04 g, 22.8 mmol, 1.25 mL, 3.00 eq). The mixture was stirred at 100 °C for 1 hour and then the reaction mixture was diluted with water (3 mL) and pH adjusted to 4-5 with sodium hydroxide (2N, 0.1 mL). The formed solid was filtered and dried under reduced pressure to give 7-hydroxyquinoline-6-carbonitrile (1.20 g, crude) as a black solid which used into next step directly without further purification. LCMS $[M+1]^+ = 171.1$.

[0287] **Step 3:** To a solution of 7-hydroxyquinoline-6-carbonitrile (500 mg, 2.94 mmol, 1 eq.) and triethylamine (0.82 mL, 5.88 mmol, 2.00 eq.) in dichloromethane (10 mL) was added trifluoromethanesulfonic anhydride (0.73 mL, 4.41 mmol, 1.50 eq.) in a dropwise fashion at 0 °C. The mixture was stirred at 20 °C for 1 hour and after such time the reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (50 mL $\times$ 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 10-50%) to give (6-cyano-7-quinolyl) trifluoromethanesulfonate (250 mg, 0.570 mmol, 19% yield) as a yellow oil. LCMS $[M+1]^+ = 303.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 9.15$ (dd, $J = 1.6, 4.0$ Hz, 1H), 8.37 (s, 1H), 8.32 - 8.30 (d, $J = 8.4$ Hz 1H), 8.23 (s, 1H), 7.65 (dd, $J = 4.0, 8.4$ Hz, 1H).

[0288] **Step 4:** A mixture of (6-cyano-7-quinolyl) trifluoromethanesulfonate (237 mg, 0.541 mmol, 1.00 eq.), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (135 mg, 0.649 mmol, 1.20 eq.), sodium bicarbonate (91 mg, 1.08 mmol, 2.00 eq.) and $\text{Pd}(\text{dtbpf})\text{Cl}_2$ (35 mg, 0.054 mmol, 0.10 eq.) in dioxane (10 mL) and water (2 mL) was degassed with nitrogen and stirred at 80 °C for 1 hour. After such time the mixture was concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 10-100%) to give 7-(2-methylpyrazol-3-yl)quinoline-6-carbonitrile (120 mg, 0.498 mmol, 92% yield) as a yellow solid. LCMS $[M+1]^+ = 235.2$.

[0289] **Step 5:** A mixture of 7-(2-methylpyrazol-3-yl)quinoline-6-carbonitrile (120 mg, 0.512 mmol, 1.00 *eq.*) and *N*-bromosuccinimide (164 mg, 0.922 mmol, 1.80 *eq.*) in acetonitrile (4 mL) was degassed with nitrogen and stirred at 20 °C for 2 hours. After such time the mixture was concentrated and the residue was purified by prep-TLC (SiO₂, dichloromethane/methyl alcohol 10%) to give 7-(4-bromo-2-methyl-pyrazol-3-yl)quinoline-6-carbonitrile (121 mg, 0.385 mmol, 75% yield) as a yellow solid. LCMS $[M+1]^+ = 314.9$; ¹H NMR (400 MHz, CDCl₃) δ = 9.15 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.43 (s, 1H), 8.33 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.23 (s, 1H), 7.68 - 7.63 (m, 2H), 3.87 (s, 3H).

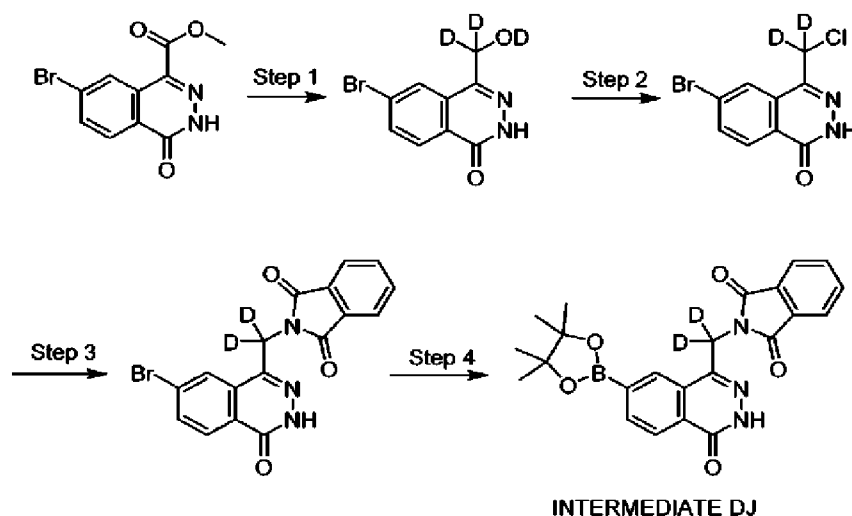
INTERMEDIATE DI



INTERMEDIATE DI

[0290] To a solution of *N*-(4-bromo-2-methyl-pyrazol-3-yl)benzamide (500 mg, 1.78 mmol, 1.00 *eq.*) in DMF (5 mL) at 0 °C was added sodium hydride (143 mg, 3.57 mmol, 60.0% purity, 2.00 *eq.*) and the mixture stirred at 0 °C for 30 minutes. After such time iodomethane (0.133 mL, 2.14 mmol, 1.20 *eq.*) in DMF (1 mL) was added and the mixture was stirred at 0 °C for a further 10 minutes. The reaction mixture was then diluted with water (50 mL) and extracted with ethyl acetate (40 mL $\times$ 3) and the combined organic extracts were washed with brine (70 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 0-30%) to give *N*-(4-bromo-2-methyl-pyrazol-3-yl)-*N*-methyl-benzamide (400 mg, 1.36 mmol, 76% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.44 (s, 1H), 7.36 - 7.41 (m, 1H), 7.26 - 7.33 (m, 4H), 3.72 (s, 3H), 3.23 (s, 3H).

INTERMEDIATE DJ



[0291] **Step 1:** To a stirred solution of methyl 7-bromo-4-oxo-3H-phthalazine-1-carboxylate (1.00 g, 3.53 mmol, 1.00 *eq.*), sodium borodeuteride (347 mg, 9.18 mmol, 2.60 *eq.*) in methanol- d_4 (30 mL) at 0 °C was added calcium chloride (470 mg, 4.24 mmol, 1.20 *eq.*). The mixture then stirred at 0 °C for 3 hours then at 20 °C for 1 hour. After such time the reaction mixture was concentrated. The residue was diluted with water (30 mL), the pH adjusted to 5 with hydrochloric acid (1N, 5 mL) and the mixture filtered and the filter cake washed with water (5 mL $\times$ 3) then triturated with ethyl alcohol (20 mL) to give 6-bromo-4-((hydroxy-d)methyl-d₂)phthalazin-1(2H)-one (463 mg, 1.61 mmol, 46% yield) as a white solid. LCMS $[M+1]^+ = 259.0$; ^1H NMR (400 MHz, DMSO- d_6) δ = 12.66 (s, 1H), 8.31 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 2.0, 8.4 Hz, 1H), 5.53 (s, 1H).

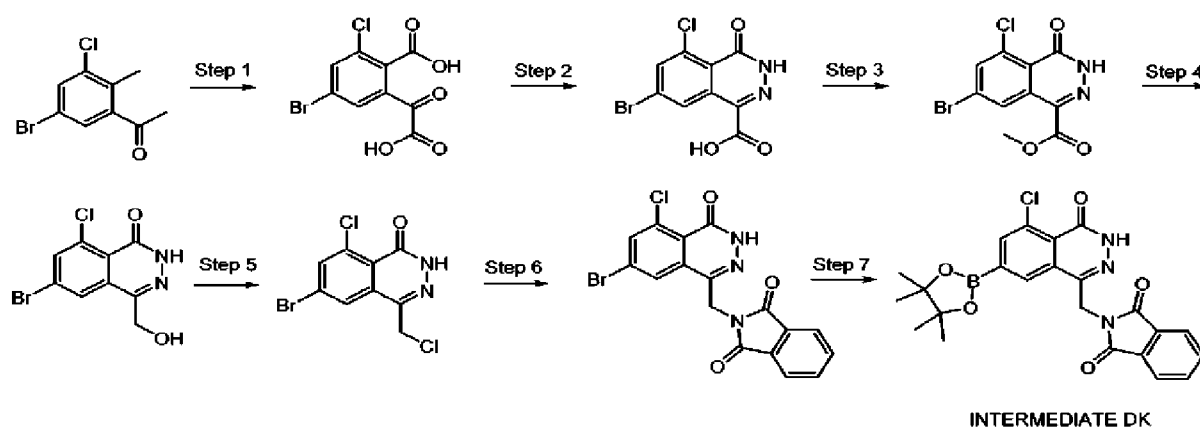
[0292] **Step 2:** A mixture of 6-bromo-4-((hydroxy-d)methyl-d₂)phthalazin-1(2H)-one (463 mg, 1.61 mmol, 1.00 *eq.*) and thionyl chloride (10 mL) was stirred at 30 °C for 12 hours. After such time the mixture was concentrated and the residue dissolved in dichloromethane and concentrated 3 times (2 mL $\times$ 3) to give 6-bromo-4-(chloromethyl-d₂)phthalazin-1(2H)-one (450 mg, 1.43 mmol, 88% yield) as a yellow solid. LCMS $[M+1]^+ = 277.0$.

[0293] **Step 3:** To a solution of 6-bromo-4-(chloromethyl-d₂)phthalazin-1(2H)-one (450 mg, 1.63 mmol, 1.00 *eq.*) in DMF (3 mL) was added (1,3-dioxoisindolin-2-yl)potassium (454 mg, 2.45 mmol, 1.50 *eq.*) and the mixture stirred at 90 °C for 2 hours. After such time the cooled reaction mixture was filtered and the collected solid was triturated with ethyl alcohol (5 mL), filtered and dried to give 2-((7-bromo-4-oxo-3,4-dihydrophthalazin-1-

yl)methyl-d2)isoindoline-1,3-dione (300 mg, crude) as a white solid. LCMS $[M+1]^+ = 386.0$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.60$ (s, 1H), 8.43 (d, $J = 1.6$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 8.09 - 8.05 (m, 1H), 7.97 - 7.92 (m, 2H), 7.92 - 7.87 (m, 2H).

[0294] **Step 4:** A mixture of 2-((7-bromo-4-oxo-3,4-dihydrophthalazin-1-yl)methyl-d2)isoindoline-1,3-dione (200 mg, crude), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (197 mg, 0.78 mmol), Pd(dppf)Cl₂ (38 mg, 0.052 mmol) and potassium acetate (152 mg, 1.55 mmol) in dioxane (10 mL) was degassed with nitrogen. The mixture was stirred at 100 °C for 2 hours and after such time the mixture was concentrated and the residue triturated with methyl alcohol (3 mL), filtered and dried to give 2-((4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl-d2)isoindoline-1,3-dione (200 mg, 0.303 mmol, 59% yield over 2 steps) as a white solid. LCMS $[M+1]^+ = 352.1$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.70 - 12.28$ (m, 1H), 8.35 - 8.25 (m, 2H), 8.13 (br s, 1H), 7.93 (br d, $J = 17.0$ Hz, 4H), 1.34 (br s, 12H).

INTERMEDIATE DK



[0295] **Step1:** To a solution of K₂CO₃ (44.7 g, 323 mmol) in water (500 mL) was added 1-(5-bromo-3-chloro-2-methylphenyl)ethan-1-one (40.0 g, 162 mmol) and warmed to 50 °C. KMnO₄ was then added carefully in 10 batches (165 g, 1.04 mol) and the temperature maintained below 80 °C to avoid an uncontrolled exotherm. After completion of the addition the mixture was stirred at 60 °C for 6 hrs. After such time the mixture was cooled to 0 °C and quenched by the dropwise addition of saturated sodium sulfite solution (200 mL) while maintaining the temperature below 10 °C. The mixture was then stirred for 30 min at 0 °C. After such time the clear colorless mixture was filtrated with celatom and the filter cake was washed with water (100 mL) and the aqueous phase washed with MTBE (200 mL). The aqueous phase was then acidified to pH 2 by the addition of 3M HCl followed by extraction

with ethyl acetate (300 mL $\times$ 3). The combined organic phases were washed with brine (300 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound 4-bromo-2-(carboxycarbonyl)-6-chlorobenzoic acid (20.0 g, 65.0 mmol, 36% yield) as white solid. LCMS [M-1]⁻ = 306.8; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.7 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H).

[0296] **Step 2:** To a solution of compound 4-bromo-2-(carboxycarbonyl)-6-chlorobenzoic acid (20.0 g, 65.0 mmol) in EtOH (200 mL) was added NH₂NH₂·H₂O (4.30 g, 85.9 mmol) in one portion under N₂. The mixture was then stirred at 70 °C for 1 hr. After such time the cooled reaction mixture was filtered, washed and the solid dried in vacuum to give 7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (14.0 g, 46.1 mmol, 71% yield) as white solid. LCMS [M+1]⁺ = 305.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 (d, *J*=2.0 Hz, 1H), 7.59 (d, *J*=2.0 Hz, 1H).

[0297] **Step 3:** To a mixture of 7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (14.0 g, 46.1 mmol) in MeOH (250 mL) was added conc. H₂SO₄ (9.23 g, 92.2 mmol) in one portion under nitrogen. The mixture was then heated to 70 °C for 16 hrs then allowed to cool to ambient temperature, filtered and dried gave methyl 7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazine-1-carboxylate (7.50 g, 23.6 mmol, 51% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.2 (s, 1H), 6.68 (d, *J*=1.6 Hz, 1H), 8.18 (d, *J*=1.6 Hz, 1H).

[0298] **Step 4:** A solution of methyl 7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazine-1-carboxylate (7.50 g, 23.6 mmol) in EtOH (70 mL) was added NaBH₄ (2.32 g, 61.4 mmol) at 0 °C followed by the careful, slow addition of CaCl₂ (3.15 g, 28.3 mmol) at 0 °C over 2 hours. The mixture was then allowed to warm to 15 °C and stirred for a further 2 hours. After such time the reaction was poured onto sat. NH₄Cl (100 mL) and the solid filtered, washed with water (10 mL) then EtOH (10 mL) and dried to give 6-bromo-8-chloro-4-(hydroxymethyl)phthalazin-1(2H)-one (4.00 g, 13.8 mmol, 54% yield) as white solid. LCMS [M+1]⁺ = 291.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.6 (s, 1H), 8.24 (d, *J*=1.6 Hz, 1H), 8.14 (d, *J*=1.6 Hz, 1H), 5.61- 5.58 (t, *J*=2 Hz, 1H), 4.65 -4.63 (d, *J*=8 Hz, 2H).

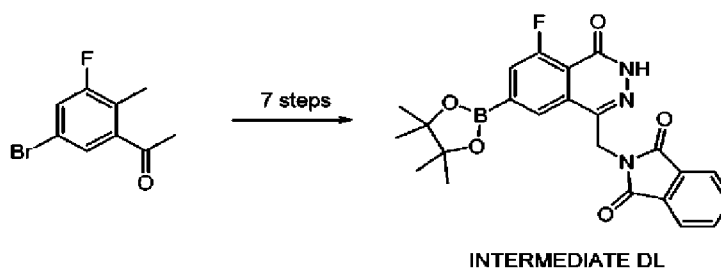
Step 5: A mixture of 6-bromo-8-chloro-4-(hydroxymethyl)phthalazin-1(2H)-one (4.00 g, 13.8 mmol) and SOCl₂ (36.4 g, 306 mmol) was stirred at 65 °C for 1 hr. After such time the mixture was concentrated, and the crude residue triturated with MTBE (30 mL) at 25 °C for 30 min. The solid was then filtered and dried to give 6-bromo-8-chloro-4-(chloromethyl)phthalazin-1(2H)-one (3.50 g, 11.4 mmol, 82% yield) as light yellow solid.

LCMS $[M+1]^+ = 309.1$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.9 (s, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 5.06 (s, 1H).

[0299] **Step 6:** To a mixture of potassium phthalimide (2.53 g, 13.6 mmol) in DMF (5 mL) was added a solution of 6-bromo-8-chloro-4-(chloromethyl)phthalazin-1(2H)-one (3.50 g, 11.3 mmol) in DMF (35 mL) at 0 °C and the mixture stirred at 0 °C for 2 hrs. After such time the mixture was poured onto ice-water (200 mL), stirred for 30 min., filtered then the solid was dried and then triturated with MeOH (30 mL) at 15 °C for 30 min. The solid was filtered and dried to give 2-((7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (1.30 g, 3.10 mmol, 27% yield) as light yellow solid. LCMS $[M+1]^+ = 420.0$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.5 (s, 1H), 8.36 (s, 1H), 8.19 (s, 1H), 7.97 - 7.94 (m, 2H), 7.92 - 7.89 (m, 2H), 5.14 (s, 2H).

[0300] **Step 7:** A mixture of 2-((7-bromo-5-chloro-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (1.30 g, 3.10 mmol), bis(pinacolato)diboron (1.20 g, 4.66 mmol) and potassium acetate (762 mg, 7.76 mmol) in dioxane (20 mL) was degassed with nitrogen. Then $\text{Pd}(\text{dppf})\text{Cl}_2$ (114 mg, 0.16 mmol) was added and the mixture stirred at 70 °C for 2.5 hrs. After such time the mixture was cooled to room temperature, filtered and the concentrated residue triturated with MeOH (30.0 mL) at 15 °C for 30 min. The solid was then filtered, washed with MTB and dried to give 2-((5-chloro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (910 mg, 1.95 mmol, 63% yield) as light yellow solid. LCMS $[M+1]^+ = 383.9$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.5 (s, 1H), 8.20 (s, 1H), 7.79 (s, 1H), 7.96 - 7.94 (m, 2H), 7.91 - 7.89 (m, 2H), 5.17 (s, 2H), 1.35 (s, 12H).

INTERMEDIATE DL

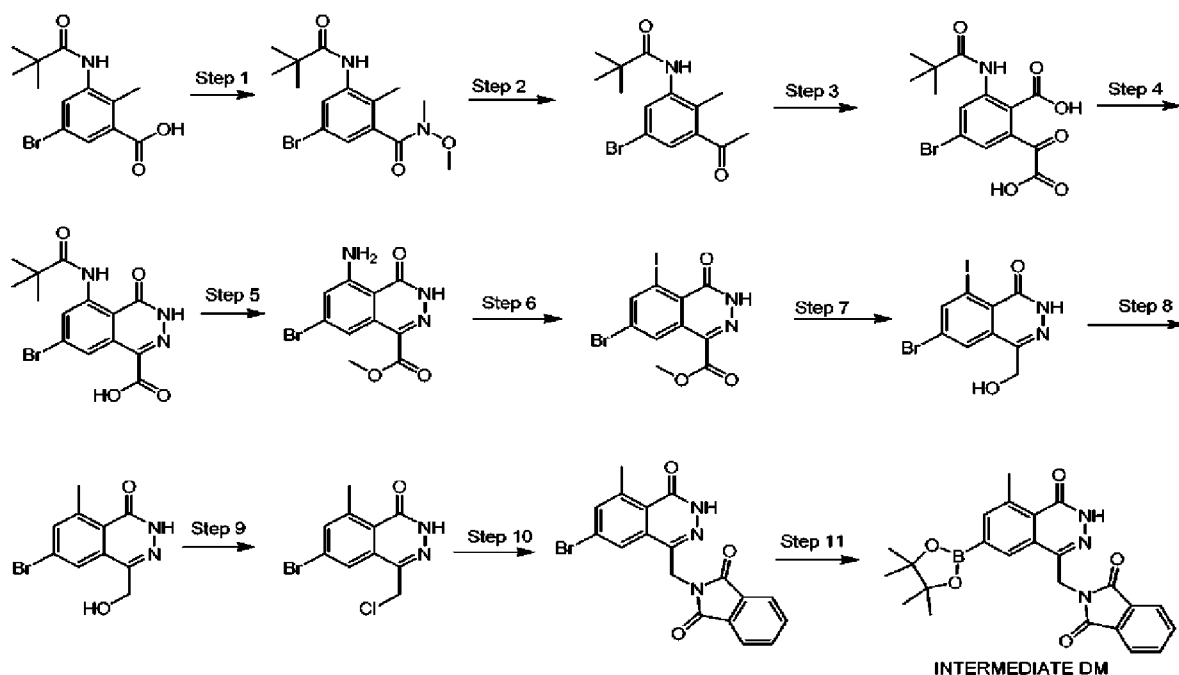


[0301] Following the same procedure for the synthesis of Intermediate DK, 2-((5-fluoro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione, Intermediate DL, was prepared as a white solid (200 mg,

0.42 mmol, 2.1% yield) in 7 steps from 1-(5-bromo-3-fluoro-2-methylphenyl)ethan-1-one.

LCMS $[M+1] = 368.1$; $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) $\delta = 12.51$ (s, 1H), 8.09 (s, 1H), 7.96 – 7.89 (m, 4H), 7.40 (d, 1H), 5.17 (s, 2H), 1.36 (s, 12H).

INTERMEDIATE DM



[0302] **Step 1:** To a solution of 5-bromo-2-methyl-3-pivalamidobenzoic acid (120 g, 382 mmol) in DMF (1.20 L) was added DIEA (98.7 g, 764 mmol, 133 mL), HATU (189 g, 497 mmol), followed by *N,O*-dimethylhydroxylamine (55.9 g, 573 mmol, HCl) at 20°C. The resulting solution was stirred at 20°C for 2 hrs and after such time the reaction mixture was poured into ice water (5.0 L). The mixture was extracted with ethyl acetate (2.0 L $\times$ 3) and the combined organic phase was washed with brine (1.0 L), dried with anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure to dry to afford 5-bromo-*N*-methoxy-*N*,2-dimethyl-3-pivalamidobenzamide (135 g, 378 mmol, 99% yield) as brown oil. $^1\text{H NMR}$: 400 MHz, $\text{DMSO}-d_6$ δ 9.06 (s, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.35 (d, $J = 2.0$ Hz, 1H), 3.43 (s, 3H), 3.27 (s, 3H), 2.01 (s, 3H), 1.23 (s, 9H).

[0303] **Step 2:** To a solution of 5-bromo-*N*-methoxy-*N*,2-dimethyl-3-pivalamidobenzamide (135 g, 378 mmol) in THF (1.5 L) was added MeMgBr (3.0 M, 315 mL) at 0°C. The resulting solution was allowed to warm to 20°C and stirred for 12 hrs. After such time an additional aliquot of MeMgBr (3 M, 63.0 mL) was added and the mixture stirred for a further

4 hrs. The mixture was then diluted with NH_4Cl (1.5 L), extracted with ethyl acetate (1.0 L $\times$ 3) and the combined organic phases were washed with brine (1.0 L), dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford N-(3-acetyl-5-bromo-2-methylphenyl)pivalamide (115 g, 368 mmol, 98% yield) as yellow solid. ^1H NMR 400 MHz, $\text{DMSO}-d_6$ δ 9.10 (s, 1H), 7.75 (d, $J = 2.0$ Hz, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 2.55 (s, 3H), 2.10 (s, 3H), 1.23 (s, 9H).

[0304] **Step 3:** To a solution of N-(3-acetyl-5-bromo-2-methylphenyl)pivalamide (57.5 g, 184 mmol) in H_2O (600 mL) was added K_2CO_3 (50.9 g, 368 mmol) and KMnO_4 (204 g, 1.29 mol) at 50 °C. The reaction solution was stirred at 50 °C for 17 hrs. After such time the reaction mixture was quenched by saturated sodium thiosulfate solution and filtered through diatomite. The pH was adjusted to 2 with 2N HCl and the mixture extracted with an ethyl acetate:THF 10:1 mixture (1.00 L $\times$ 3), washed with brine (500 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 4-bromo-2-(carboxycarbonyl)-6-pivalamidobenzoic acid (58.0 g, crude) as light yellow oil. ^1H NMR 400 MHz, $\text{DMSO}-d_6$ δ 9.87 (s, 1H), 8.63 (d, $J = 2.0$ Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 1.27 (s, 9H).

[0305] **Step 4:** To a solution of 4-bromo-2-(carboxycarbonyl)-6-pivalamidobenzoic acid (110 g, 296 mmol) in EtOH (1.10 L) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (18.1 g, 355 mmol, 17.6 mL) and the solution was stirred at 75 °C for 3 hrs. After such time the reaction mixture was filtered and the filter cake dried to give 7-bromo-4-oxo-5-pivalamido-3,4-dihydrophthalazine-1-carboxylic acid (30.0 g, 81.5 mmol, 28% yield) as white solid. ^1H NMR 400 MHz, $\text{DMSO}-d_6$ δ 13.0 (s, 1H), 9.06 (d, $J = 2.0$ Hz, 1H), 8.18 (d, $J = 2.0$ Hz, 1H), 1.27 (s, 9H).

[0306] **Step 5:** To a solution of 7-bromo-4-oxo-5-pivalamido-3,4-dihydrophthalazine-1-carboxylic acid (30.0 g, 81.5 mmol) in MeOH (400 mL) was added a solution of HCl/MeOH (4 M, 400 mL). The reaction mixture was warmed to 70 °C and stirred for 36 hrs to form a yellow solid. The reaction was concentrated, diluted with water (100 mL) and the pH adjusted to pH 8 with 1 N NaOH , stirred for 0.5 hr then filtered. The filter cake was washed with water (50 mL) then EtOH (100 mL) and dried to give the crude product methyl 5-amino-7-bromo-4-oxo-3,4-dihydrophthalazine-1-carboxylate (20.0 g, crude) as a yellow solid.

[0307] **Step 6:** To a solution of methyl 5-amino-7-bromo-4-oxo-3,4-dihydrophthalazine-1-carboxylate (15.0 g, 50.3 mmol) in MeCN (500 mL) was added TosOH (34.6 g, 200 mmol) at 0 °C under N_2 . To this solution was added a solution of NaNO_2 (8.68 g, 125 mmol) in H_2O (20 mL) and the mixture was stirred at 0 °C for 10 minutes then a solution of KI (25.0 g, 150

mmol) in H₂O (20.0 mL) was added dropwise. The mixture was stirred at 20 °C for 1 hr and the reaction was quenched by Na₂S₂O₃. The mixture was concentrated to remove the MeCN then diluted with water (200 mL) and filtered. The filter cake was washed with water (50 mL) then EtOH (100 mL) and dried to give the methyl 7-bromo-5-iodo-4-oxo-3,4-dihydrophthalazine-1-carboxylate (15.0 g, crude) as a yellow solid.

[0308] **Step 7:** In 8 batches a solution of methyl 7-bromo-5-iodo-4-oxo-3,4-dihydrophthalazine-1-carboxylate (4.00 g, 9.78 mmol) in EtOH (60 mL) was added NaBH₄ (740 mg, 19.6 mmol) in batches at 0 °C followed by the addition of CaCl₂ (1.30 g, 11.7 mmol) in batches at 0 °C. The reaction was stirred at 20 °C for 1 hr. The 8 batches were then combined and quenched with NH₄Cl (200 mL). The mixture was concentrated to remove EtOH, diluted with water (200 mL) and then filtered and the filter cake was washed with water (100 mL) and dried. The residue was triturated in MeOH (200 mL) for 10 hrs, filtered and dried to give the 6-bromo-4-(hydroxymethyl)-8-iodophthalazin-1(2H)-one (19.0 g, 38.9 mmol, 50% yield) as a yellow solid. ¹H NMR 400 MHz, DMSO-*d*₆ δ 12.64 (s, 1H), 8.56 (d, J = 1.88 Hz, 1H), 8.29 (d, J = 1.88 Hz, 1H), 5.62 - 5.54 (m, 1H), 4.62 (d, J = 5.70 Hz, 2H).

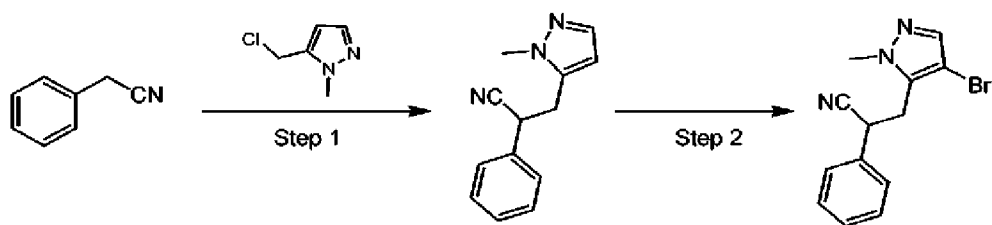
[0309] **Step 8:** In three batches, to a mixture of 6-bromo-4-(hydroxymethyl)-8-iodophthalazin-1(2H)-one (2.00 g, 5.25 mmol) in dioxane (40 mL) was added a solution of 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in THF (3.67 mL, 13.1 mmol, 50% purity), Cs₂CO₃ (4.28 g, 13.1 mmol) and Pd(dppf)Cl₂ (384 mg, 524 μmol). The reaction was stirred at 100 °C for 10 hrs. The three batches were combined and filtered through diatomite. The filtrate was concentrated and the residue purified by Prep-HPLC (Phenomenex luna C18 250 x 150 mm x 15 μm; mobile phase: [water (0.1% TFA) - MeOH]; B%: 30% - 60%, 20 min) to give the 6-bromo-4-(hydroxymethyl)-8-methylphthalazin-1(2H)-one (1.1 g, 4.06 mmol, 26% yield) as a light yellow solid. LCMS [M+1]⁺ = 271; ¹H NMR 400 MHz, DMSO-*d*₆ δ 12.44 (s, 1H), 8.10 (s, 1H), 7.82 (s, 1H), 4.63 (s, 3H), 2.81 (s, 3H).

[0310] **Step 9:** A solution of 6-bromo-4-(hydroxymethyl)-8-methylphthalazin-1(2H)-one (1.20 g, 4.46 mmol) in SOCl₂ (13 mL) was stirred at 70°C for 2 hr. After such time the mixture was concentrated and the residue triturated in petroleum ether for 0.5 hr, filtered and dried to give 6-bromo-4-(chloromethyl)-8-methylphthalazin-1(2H)-one (1.20 g, 4.17 mmol, 94% yield) as a light yellow solid. LCMS [M+1]⁺ = 289; ¹H NMR 400 MHz, DMSO-*d*₆ δ 12.70 (s, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 5.03 (s, 2H), 2.81 (s, 3H).

[0311] **Step 10:** To a mixture of give 6-bromo-4-(chloromethyl)-8-methylphthalazin-1(2H)-one (1.10 g, 3.83 mmol) in DMF (30 mL) was added potassium isoindoline-1,3-dione (850 mg, 4.59 mmol) in one portion at 0 °C under N₂. The mixture was stirred at 25 °C for 1 hr and after such time the mixture was slowly poured into ice water (100 mL) and the formed white solid was filtrated, washed with water and dried to give the crude product 2-((7-bromo-5-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (1.10 g, 2.32 mmol, 61% yield) as a white solid. LCMS $[M+1]^+ = 400$; ¹H NMR 400 MHz, DMSO-*d*₆ δ 12.37 (s, 1H), 8.20 (d, *J* = 1.32 Hz, 1H), 7.97 - 7.87 (m, 5H), 5.12 (s, 2H), 2.81 (s, 3H).

[0312] **Step 11:** 2-((7-bromo-5-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (1.10 g, 2.76 mmol), Pd(dppf)Cl₂ (202 mg, 276 μ mol), KOAc (542 mg, 5.52 mmol) and bis(pinacolato)diboron (1.05 g, 4.14 mmol) in dioxane (20 mL) was de-gassed with nitrogen then heated at 80 °C for 10 hours. After such time the reaction was filtered through diatomite and the cake washed with MeOH (10 mL) and the filtrate concentrated. The residue was then triturated with MeOH (10 mL) for 1 hr, filtered and the filter cake washed with MeOH and dried to give 2-((5-methyl-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione, Intermediate DM (510 mg, 1.15 mmol, 42% yield) as a gray solid. LCMS: Boronic acid $[M+1]^+ = 364$; boronate ester $[M+1]^+ = 446$. ¹H NMR 400 MHz, DMSO-*d*₆ δ 12.27 (s, 1H), 8.06 (s, 1H), 7.92 - 7.82 (m, 5H), 5.11 (s, 2H), 2.80 (s, 3H), 1.31 (s, 12H).

INTERMEDIATE DN



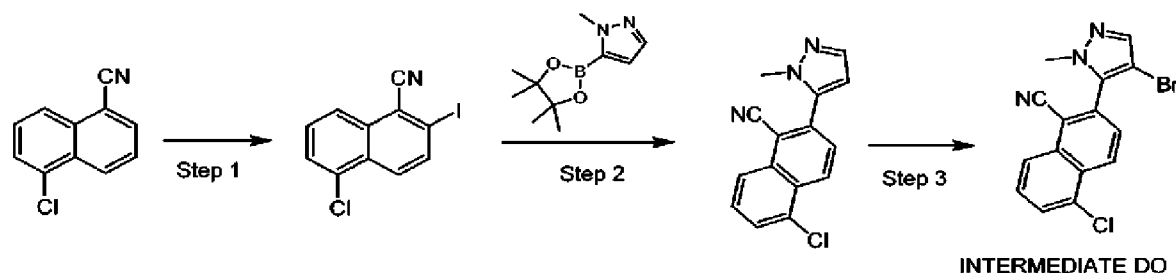
INTERMEDIATE DN

[0313] **Step 1:** To a solution of 5-(chloromethyl)-1-methyl-pyrazole (584 mg, 3.50 mmol, 1.00 *eq*) and 2-phenylacetonitrile (819 mg, 6.99 mmol, 2.00 *eq*.) in DMF (10 mL) was added potassium carbonate (966 mg, 6.99 mmol, 2.00 *eq*.). The mixture was stirred at 120 °C for 4 hours then and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate 10-50%) to give 3-(2-methylpyrazol-3-yl)-2-phenyl-propanenitrile (300 mg, 1.42 mmol, 41% yield) as a brown oil. LCMS $[M+1]^+ =$

212.0; ^1H NMR (400 MHz, CDCl_3) δ = 7.35 - 7.22 (m, 4H), 7.18 - 7.10 (m, 2H), 6.11 (d, J = 1.6 Hz, 1H), 3.98 (t, J = 6.8 Hz, 1H), 3.41 (s, 3H), 3.26 - 3.18 (m, 1H), 3.16 - 3.05 (m, 1H).

[0314] **Step 2:** To a mixture of 3-(2-methylpyrazol-3-yl)-2-phenyl-propanenitrile (160 mg, 0.76 mmol, 1.00 *eq.*) in dry acetonitrile (2.0 mL) was added NBS (121 mg, 0.68 mmol, 0.90 *eq.*) in several portions. The mixture was stirred at 15 °C for 2 hours. After such time ethyl acetate (40 mL) and water (40 mL) were added and the layers separated. The aqueous phase was extracted with ethyl acetate (30 mL $\times$ 2) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (Phenomenex Gemini-NX C18 75 $\times$ 30 mm $\times$ 3 μm ; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to give 3-(4-bromo-2-methyl-pyrazol-3-yl)-2-phenyl-propanenitrile (90.0 mg, 0.31 mmol, 41% yield) as a yellow oil. LCMS $[\text{M}+1]^+ = 289.8$; ^1H NMR (400 MHz, CDCl_3) δ = 7.37 (s, 1H), 7.35 - 7.26 (m, 3H), 7.20 - 7.14 (m, 2H), 4.04 (t, J = 7.6 Hz, 1H), 3.40 (s, 3H), 3.30 (dd, J = 7.2, 14.8 Hz, 1H), 3.07 (dd, J = 8.0, 14.8 Hz, 1H).

INTERMEDIATE DO



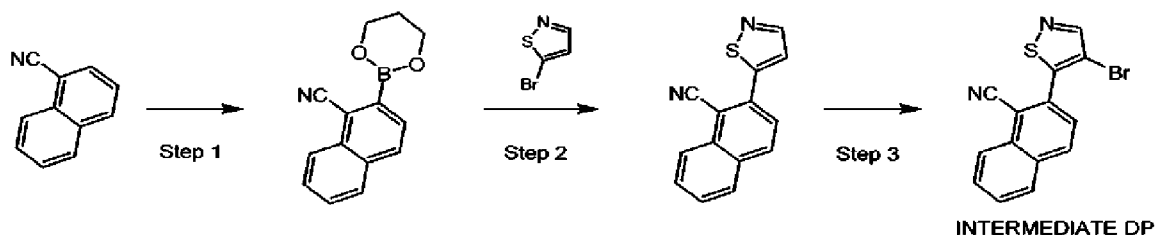
[0315] **Step 1:** *n*-Butyllithium (2.5 M in hexane, 959 μL , 1.50 *eq.*) was added dropwise over 5 minutes to a solution of 2,2,6,6-tetramethylpiperidine (2.40 mmol, 407 μL , 1.50 *eq.*) in THF (3 mL) maintained at 0 °C. After 30 minutes, the reaction mixture was cooled to -78 °C and a solution of 5-chloronaphthalene-1-carbonitrile (300 mg, 1.60 mmol, 1.00 *eq.*) in THF (1.00 mL) was added dropwise over 10 minutes. The resulting dark solution was maintained at -78 °C for 2 hours. A solution of iodine (609 mg, 2.40 mmol, 1.50 *eq.*) in THF (3 mL) was then added dropwise over 10 minutes. The reaction mixture was maintained at -78 °C for 2 hours then allowed to warm to 20 °C for 3 hours. The reaction mixture was quenched with water (1 mL) and the resulting mixture diluted with ethyl acetate (150 mL). The mixture was washed successively with saturated aqueous sodium thiosulfate (3 $\times$ 150 mL), 1 M HCl (2 $\times$ 150 mL), and brine (1 $\times$ 150 mL). The organic layer was dried over anhydrous sodium

sulfate, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5%) to give 5-chloro-2-iodo-1-naphthonitrile (180 mg, 574 μ mol, 36% yield) as a yellow solid. GCMS $[M+H]^+ = 312.9$; ¹H NMR (400 MHz, CDCl₃) δ = 8.55 (d, J = 8.8 Hz, 1H), 8.01 - 7.97 (m, 1H), 7.73 - 7.69 (m, 1H), 7.67 - 7.64 (m, 1H), 7.63 - 7.58 (m, 1H).

[0316] **Step 2:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (104 mg, 498 μ mol, 1.30 *eq.*), 5-chloro-2-iodo-1-naphthonitrile (120 mg, 383 μ mol, 1.00 *eq.*), Pd(dtbpf)Cl₂ (25 mg, 38 μ mol, 0.10 *eq.*) and sodium carbonate (81 mg, 766 μ mol, 2.00 *eq.*) in the dioxane (3 mL) and water (0.6 mL) was degassed with nitrogen then stirred at 80 °C for 1 hour. The mixture was then concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate 30%) to give 5-chloro-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (90 mg, 336 μ mol, 87% yield) as a yellow solid. LCMS $[M+1]^+ = 268.2$; ¹H NMR (400 MHz, CDCl₃) δ = 8.62 (d, J = 8.8 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.81 - 7.77 (m, 1H), 7.73 - 7.67 (m, 1H), 7.67 - 7.63 (m, 2H), 6.61 (d, J = 2.0 Hz, 1H), 3.91 (s, 3H).

[0317] **Step 3:** To a solution of 5-chloro-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (170 mg, 635 μ mol, 1.00 *eq.*) in acetonitrile (3 mL) was added NBS (124 mg, 699 μ mol, 1.10 *eq.*). The mixture was stirred at 35 °C for 2 hours then concentrated to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate 30%) to give 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-1-naphthonitrile, Intermediate DO (130 mg, 375 μ mol, 59% yield) as a white solid. LCMS $[M+1]^+ = 347.8$; ¹H NMR (400 MHz, CDCl₃) δ = 8.67 (dd, J = 0.8, 8.8 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 1.2, 7.6 Hz, 1H), 7.75 - 7.69 (m, 1H), 7.66 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H).

INTERMEDIATE DP



[0318] **Step 1:** To a solution of 2,2,6,6-tetramethylpiperidine (553 mg, 3.92 mmol, 0.67 mL, 1.20 *eq.*) in THF (7 mL) was added n-butyl lithium (2.50 M, 1.57 mL, 1.20 *eq.*) at -10 °C

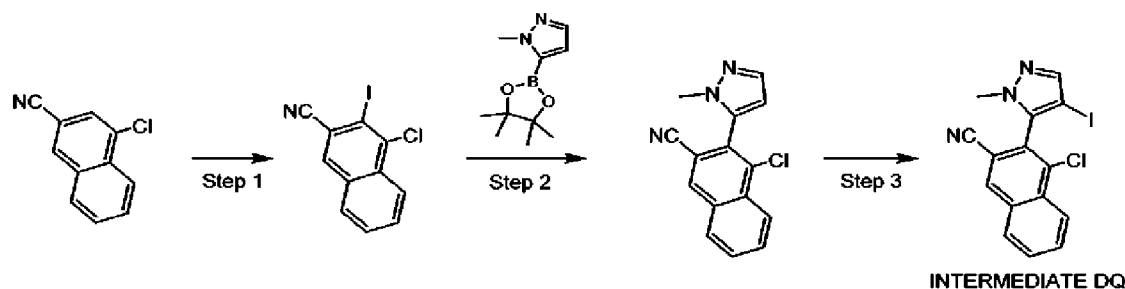
under a nitrogen atmosphere. The mixture was stirred for 10 minutes, cooled to -65 °C and triisopropyl borate (859 mg, 4.57 mmol, 1.05 mL, 1.40 *eq.*) was added. After 5 minutes, a solution of 1-naphthonitrile (500 mg, 3.26 mmol, 1.00 *eq.*) in THF (3 mL) was added in a dropwise fashion and the reaction was then allowed to warm slowly to 25 °C and then stirred for 16 hours. After such time acetic acid (392 mg, 6.53 mmol, 0.37 mL, 2.00 *eq.*) was added followed by the addition of propane-1,3-diol (994 mg, 13.1 mmol, 0.95 mL, 4.00 *eq.*) then the mixture was stirred at 25 °C for 1 hour. The reaction was then quenched by the addition of saturated ammonium chloride solution (20 mL) and then diluted with water (10 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-(1,3,2-dioxaborinan-2-yl)-1-naphthonitrile (600 mg, 2.53 mmol, 78% yield) as a light-yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.40 (d, *J* = 8.0 Hz, 1H), 8.04 - 8.00 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.71 - 7.60 (m, 2H), 4.30 (t, *J* = 5.6 Hz, 4H), 2.17 (quin, *J* = 5.6 Hz, 2H).

[0319] **Step 2:** To a solution of 5-bromoisothiazole (150 mg, 0.915 mmol, 1.00 *eq.*) and 2-(1,3,2-dioxaborinan-2-yl)-1-naphthonitrile (217 mg, 0.915 mmol, 1.00 *eq.*) in toluene (8 mL) and ethyl alcohol (0.8 mL) were added aqueous potassium carbonate (2.00 M, 0.915 mL, 2.00 *eq.*) and Pd(PPh₃)₄ (106 mg, 0.091 mmol, 0.10 *eq.*) at 20 °C under a nitrogen atmosphere. The mixture was stirred at 100 °C for 16 hours, concentrated to dryness and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-15%) to give 2-(isothiazol-5-yl)-1-naphthonitrile (200 mg, 0.85 mmol, 93% yield) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.62 (d, *J* = 1.6 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.79 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.74 - 7.66 (m, 2H).

[0320] **Step 3:** To a solution of 2-(isothiazol-5-yl)-1-naphthonitrile (100 mg, 0.42 mmol, 1.00 *eq.*) in acetonitrile (2 mL) was added *N*-bromo-succinimide (753 mg, 4.23 mmol, 10.0 *eq.*) at 20 °C and the mixture was stirred at 100 °C for 48 hours in a sealed tube. The mixture was then concentrated under reduced pressure and the residue diluted with ethyl acetate (30 mL) and washed with water (30 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was then purified by prep-HPLC (Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 45% - 75%, 8 min) to give 2-(4-bromoisothiazol-5-yl)-1-naphthonitrile (50 mg, 0.16 mmol, 38% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.51 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 8.8

Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.81 (dt, $J = 1.2, 7.6$ Hz, 1H), 7.77 - 7.69 (m, 1H), 7.59 (d, $J = 8.4$ Hz, 1H).

INTERMEDIATE DQ



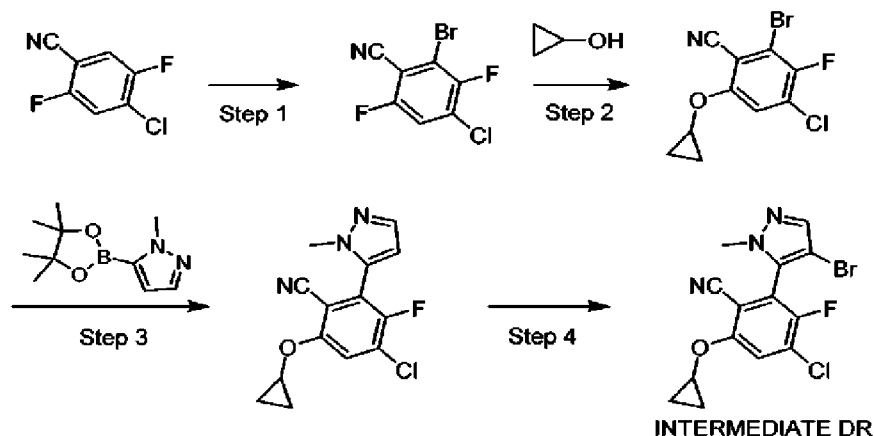
[0321] **Step 1:** To a solution of LDA (2.00 M, 0.587 mL, 1.10 *eq.*) in THF (10 mL) was added in a dropwise fashion a solution of 4-chloro-2-naphthonitrile (200 mg, 1.07 mmol, 1.00 *eq.*) in THF (5 mL) at -78 °C. Then the mixture was stirred at -78 °C for 1 hour. After such time a solution of iodine (285 mg, 1.12 mmol, 1.05 *eq.*) in THF (2 mL) was added dropwise at -78 °C. The mixture was then allowed to warm to room temperature and stirred at 20 °C for 2 hours. After such time the reaction mixture was quenched by adding saturated ammonium chloride solution (15 mL) and saturated sodium hyposulfite solution (10 mL $\times$ 3). The mixture was then extracted with ethyl acetate (20 mL $\times$ 2) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by flash chromatography (SiO₂, petroleum ether: ethyl acetate 0-5%) to give 4-chloro-3-iodo-2-naphthonitrile (200 mg, 0.606 mmol, 30% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (d, $J = 8.4$ Hz, 1H), 8.13 (s, 1H), 7.93 - 7.87 (m, 1H), 7.77 (ddd, $J = 1.2, 7.2, 8.4$ Hz, 1H), 7.72 - 7.65 (m, 1H).

[0322] **Step 2:** To a solution of 4-chloro-3-iodo-2-naphthonitrile (320 mg, 1.02 mmol, 1.00 *eq.*) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (319 mg, 1.53 mmol, 1.50 *eq.*) in dioxane (30 mL) and water (6 mL) was added potassium carbonate (283 mg, 2.04 mmol, 2.00 *eq.*) and Pd(dppf)Cl₂ (75 mg, 0.102 mmol, 0.10 *eq.*) at 25 °C. The mixture was degassed with nitrogen then stirred at 100 °C for 16 hours. The reaction mixture was then quenched with water (20 mL) and extracted with ethyl acetate (30 mL $\times$ 4). The combined organic layers were washed with brine (25 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by flash chromatography (SiO₂, petroleum ether: ethyl acetate 0-5%) to give 4-chloro-3-(1-methyl-1H-pyrazol-5-yl)-2-naphthonitrile (50 mg, 0.178 mmol, 30% yield) as a yellow solid. LCMS $[M+1]^+ =$

268.0/270.0; ^1H NMR (400 MHz, CDCl_3) δ = 8.48 - 8.39 (m, 1H), 8.34 - 8.27 (m, 1H), 8.04 - 7.95 (m, 1H), 7.90 - 7.81 (m, 1H), 7.78 (br t, J = 7.6 Hz, 1H), 7.70 - 7.63 (m, 1H), 6.52 - 6.43 (m, 1H), 3.80 - 3.72 (m, 3H).

[0323] **Step 3:** To a solution of 4-chloro-3-(1-methyl-1*H*-pyrazol-5-yl)-2-naphthonitrile (100 mg, 0.374 mmol, 1.00 *eq.*) in acetonitrile (10 mL) was added *N*-iodosuccinimide (504 mg, 2.24 mmol, 6.00 *eq.*) at 25 °C and the mixture was stirred at 80 °C for 16 hours. After such time the reaction mixture was quenched with water (2 mL) at 0 °C, and then extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated. The formed residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 30%) to give 4-chloro-3-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2-naphthonitrile (50 mg, 0.121 mmol, 32% yield) as a white solid. LCMS $[\text{M}+1]^+$ = 393.9/395.9; ^1H NMR (400 MHz, CDCl_3) δ = 8.46 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.92 - 7.86 (m, 1H), 7.84 - 7.79 (m, 1H), 7.71 (s, 1H), 3.81 (s, 3H).

INTERMEDIATE DR



[0324] **Step 1:** A mixture of 4-chloro-2,5-difluoro-benzonitrile (2.00 g, 11.5 mmol, 1.00 *eq.*), *N*-bromosuccinimide (4.10 g, 23.1 mmol, 2.00 *eq.*), palladium acetate (259 mg, 1.15 mmol, 0.10 *eq.*) and *p*-toluene sulphonic acid (992 mg, 5.76 mmol, 0.50 *eq.*) in dichloroethane (50 mL) was degassed with nitrogen then stirred at 75 °C for 12 hours. After such time the cooled mixture was extracted with dichloromethane (50 mL $\times$ 3), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and the residue purified by column chromatography (SiO_2 , petroleum ether: ethyl

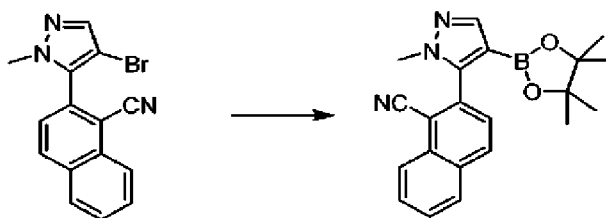
acetate 0-3%) to give 2-bromo-4-chloro-3,6-difluoro-benzonitrile (1.10 g, 4.36 mmol, 38% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.38 - 7.31 (m, 1H).

[0325] **Step 2:** A mixture of 2-bromo-4-chloro-3,6-difluoro-benzonitrile (1.10 g, 4.36 mmol, 1.00 *eq.*), cyclopropanol (380 mg, 6.54 mmol, 1.50 *eq.*) and potassium carbonate (1.51 g, 10.9 mmol, 2.50 *eq.*) in DMF (10 mL) was degassed with nitrogen then stirred at 75 °C for 2 hours. After such time the mixture was concentrated and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 7%) to give 2-bromo-4-chloro-6-(cyclopropoxy)-3-fluoro-benzonitrile (600 mg, 2.07 mmol, 47% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.36 (d, J = 5.6 Hz, 1H), 3.88 - 3.79 (m, 1H), 0.91 (d, J = 4.8 Hz, 4H).

[0326] **Step 3:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.29 g, 6.20 mmol, 3.00 *eq.*), 2-bromo-4-chloro-6-(cyclopropoxy)-3-fluoro-benzonitrile (600 mg, 2.07 mmol, 1.00 *eq.*), aqueous sodium bicarbonate (694 mg, 8.26 mmol, 0.321 mL, 4.00 *eq.*), *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (135 mg, 0.207 mmol, 0.10 *eq.*) in dioxane (20 mL) and water (4 mL) was degassed with nitrogen and the mixture was stirred at 80 °C for 16 hours. After such time the mixture was concentrated and the residue purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 5-20%) to give 4-chloro-6-(cyclopropoxy)-3-fluoro-2-(2-methylpyrazol-3-yl)benzonitrile (180 mg, 0.524 mmol, 25% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 292.1$; ^1H NMR (400 MHz, CDCl_3) δ = 7.62 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 6.0 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 3.92 - 3.85 (m, 1H), 3.81 (d, J = 1.2 Hz, 3H), 0.96 - 0.92 (m, 4H).

[0327] **Step 4:** A mixture of 4-chloro-6-(cyclopropoxy)-3-fluoro-2-(2-methylpyrazol-3-yl)benzonitrile (180 mg, 0.617 mmol, 1.00 *eq.*) and *N*-bromosuccinimide (220 mg, 1.23 mmol, 2.00 *eq.*) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours under a nitrogen atmosphere. After such time the mixture was concentrated and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 20%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-4-chloro-6-(cyclopropoxy)-3-fluoro-benzonitrile (170 mg, 0.455 mmol, 74% yield) as a white solid. LCMS $[\text{M}+1]^+ = 371.8$; ^1H NMR (400 MHz, CDCl_3) δ = 7.61 (s, 1H), 7.55 (d, J = 6.0 Hz, 1H), 3.93 - 3.85 (m, 1H), 3.80 (s, 4H), 0.97 - 0.94 (m, 4H).

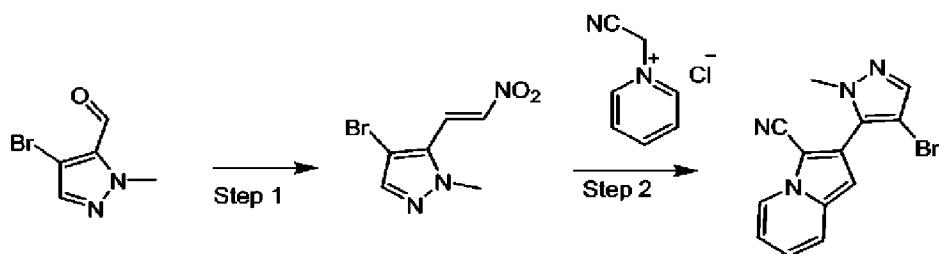
INTERMEDIATE DS



INTERMEDIATE DC

[0328] A mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (150 mg, 0.48 mmol, 1.00 *eq.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (134 mg, 0.528 mmol, 1.10 *eq.*), potassium acetate (141 mg, 1.44 mmol, 3.00 *eq.*) and *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (31.3 mg, 0.048 mmol, 0.10 *eq.*) in dioxane (3 mL) was degassed with nitrogen and then stirred at 80 °C for 2 hours. After such time the reaction mixture was concentrated under reduced pressure to give 2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]naphthalene-1-carbonitrile (160 mg, crude) as brown liquid which used into the next step without further purification. LCMS $[M+1]^+ = 360.2$.

INTERMEDIATE DT



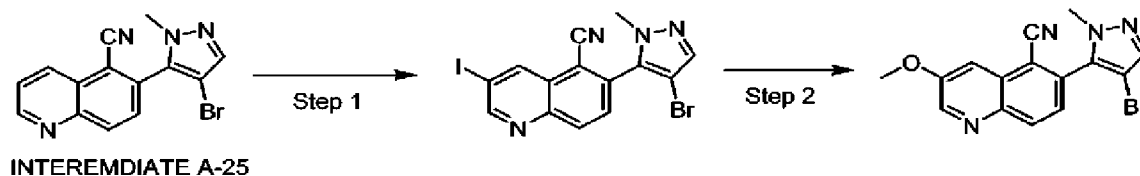
INTERMEDIATE DT

[0329] **Step 1:** To a solution of 4-bromo-2-methyl-pyrazole-3-carbaldehyde (1.00 g, 5.29 mmol, 1.00 *eq.*) and nitromethane (420 mg, 6.88 mmol, 0.37 mL, 1.30 *eq.*) in methanol (10 mL) was added in a dropwise fashion a solution of sodium hydroxide (466 mg, 11.6 mmol, 2.20 *eq.*) in water (1 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for 0.5 hour. After such time the reaction mixture was quenched by addition of HCl (1.00 M, 5 mL), filtered and the filtrate concentrated under reduced pressure to give 4-bromo-1-methyl-5-[(*E*)-2-nitrovinyl]pyrazole (627 mg, crude) as a yellow solid which used into the next step without

further purification. ^1H NMR (400 MHz, CDCl_3) δ = 8.10 (d, J = 13.6 Hz, 1H), 7.93 (d, J = 13.6 Hz, 1H), 7.57 (s, 1H), 4.03 (s, 3H).

[0330] **Step 2:** A suspension of 2-pyridin-1-ium-1-ylacetonitrile chloride (627 mg) and 4Å MS (1.00 g, 0.215 mmol) in dichloroethane (30 mL) was cooled to 0 °C then 2,6-lutidine (1.45 g, 13.5 mmol, 1.57 mL, 5.00 *eq.*) was added. After stirring for 15 minutes, 4-bromo-1-methyl-5-[(*E*)-2-nitrovinyl]pyrazole (627 mg, 2.70 mmol, 1.00 *eq.*) was added, followed by the addition of cupric acetate (736 mg, 4.05 mmol, 1.50 *eq.*). This mixture was then stirred at 0 °C for 15 minutes then warmed to 25 °C and stirred at 25 °C for 5 hours. After such time the reaction mixture was diluted with water (300 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10-20%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)indolizine-3-carbonitrile (380 mg, 1.26 mmol, 47% yield) as a yellow solid. LCMS $[\text{M} + 1]^+ = 301.0$; ^1H NMR (400 MHz, CDCl_3) δ = 8.34 (d, J = 6.0 Hz, 1H), 7.62 - 7.53 (m, 2H), 7.18 - 7.11 (m, 1H), 6.96 (dt, J = 1.2, 6.8 Hz, 1H), 6.62 (s, 1H), 3.91 (s, 3H).

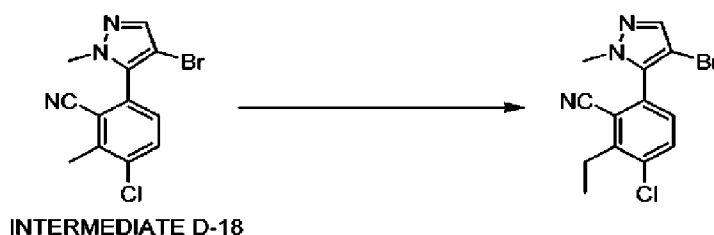
INTERMEDIATE DU



[0331] **Step 1:** A mixture of 6-(4-bromo-1-methyl-1H-pyrazol-5-yl)quinoline-5-carbonitrile, Intermediate A-25 (120 mg, 0.38 mmol, 1.00 *eq.*), *N*-iodosuccinimide (517 mg, 2.30 mmol, 6.00 *eq.*) in acetic acid (5 mL) was stirred at 80 °C for 48 hours under a nitrogen atmosphere. The mixture was then concentrated and to the residue was added saturated sodium sulfite solution (10 mL). The mixture was then extracted with ethyl acetate (5 mL) and the organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 50%) to give 6-(4-bromo-1-methyl-1H-pyrazol-5-yl)-3-iodoquinoline-5-carbonitrile (38 mg, 0.086 mmol, 22% yield) as a white solid. LCMS $[\text{M} + 1]^+ = 441.1$; ^1H NMR (400 MHz, CDCl_3) δ = 9.26 (d, J = 2.0 Hz, 1H), 9.03 (dd, J = 0.8, 2.0 Hz, 1H), 8.43 (dd, J = 0.8, 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 3.87 (s, 3H).

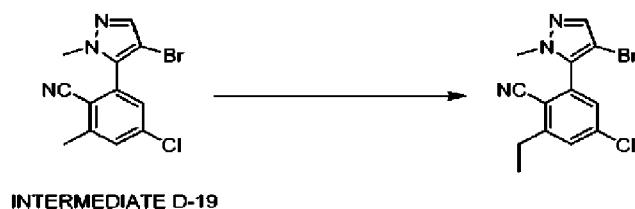
[0332] **Step 2:** A mixture of 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-iodoquinoline-5-carbonitrile (35 mg, 0.080 mmol, 1.00 *eq.*), sodium methoxide (13 mg, 0.24 mmol, 3.00 *eq.*), cuprous iodide (1.5 mg, 0.008 mmol, 0.10 *eq.*) in methanol (1 mL) was degassed with nitrogen then stirred at 105 °C for 16 hours. After such time the mixture was filtered and the filtrate concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 50%) to give 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-methoxyquinoline-5-carbonitrile (12 mg, 0.035 mmol, 44% yield) as a white solid. LCMS [M+1]⁺ = 345.1; ¹H NMR (400 MHz, CDCl₃) δ = 8.86 (d, *J* = 2.8 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 2.8 Hz, 1H), 7.66 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 4.07 (s, 3H), 3.87 (s, 3H).

INTERMEDIATE DV



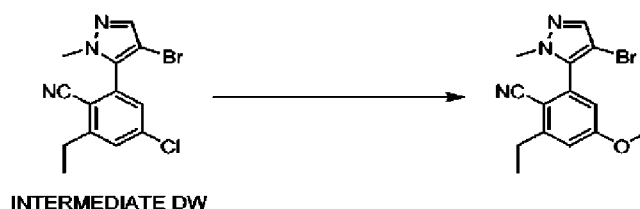
[0333] A mixture of 6-(4-bromo-2-methyl-pyrazol-3-yl)-3-chloro-2-methyl-benzonitrile, Intermediate D-18 (400 mg, 1.29 mmol, 1.00 *eq.*) in THF (5 mL) was added lithium diisopropyl amine (2.00 M, 1.29 mL, 2.00 *eq.*) at -78 °C and stirred at -78 °C for 30 minutes. Then methyl iodide (5.15 mmol, 0.32 mL, 4.00 *eq.*) was added at -78 °C and the mixture stirred for 2 hours. The reaction mixture was then quenched with ammonium chloride solution (10 mL) and extracted with dichloromethane (20 mL × 3) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 20%) to give 6-(4-bromo-2-methyl-pyrazol-3-yl)-3-chloro-2-ethyl-benzonitrile (280 mg, 0.86 mmol, 67% yield) as a yellow oil. LCMS [M+1]⁺ = 326.0; ¹H NMR (400 MHz, CDCl₃) δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.14 - 3.11 (m, 2H), 1.35 - 1.32 (m, 3H).

INTERMEDIATE DW



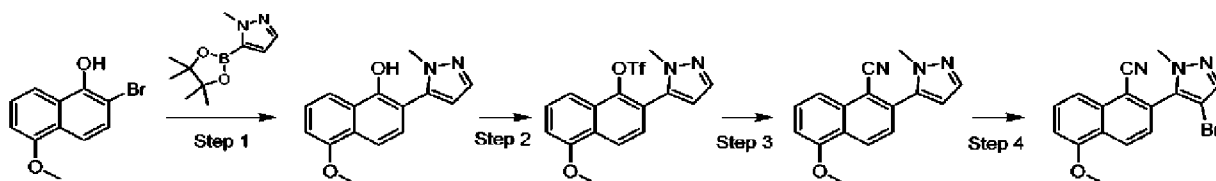
[0334] 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-ethylbenzonitrile was prepared using the same method as for the preparation of Intermediate DV using Intermediate D-19 in place of Intermediate D-18 as a white solid (30 mg, 0.074 mmol, 23%). LCMS $[M+1]^+ = 419.2$; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) $\delta = 12.88$ (s, 1H), 8.38 (br s, 3H), 8.28 (s, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 2.0$ Hz, 1H), 7.82 (d, $J = 2.0$ Hz, 1H), 7.75 (d, $J = 1.2$ Hz, 1H), 7.42 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.39 - 4.22 (m, 2H), 3.75 (s, 3H), 2.83 (q, $J = 7.6$ Hz, 2H), 1.21 (t, $J = 7.6$ Hz, 3H).

INTERMEDIATE DX



[0335] To a mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)-4-chloro-6-ethyl-benzonitrile, Intermediate DW (270 mg, 0.83 mmol, 1.00 *eq.*) in methanol (2 mL) was added sodium methoxide (449 mg, 8.32 mmol, 10.0 *eq.*) in one portion at 20 °C under nitrogen atmosphere. The mixture was stirred at 100 °C for 2 hours in a sealed tube and a light-yellow solution was formed. The mixture was then concentrated and the residue taken up in ethyl acetate (10 mL) and water (5 mL). The layers were separated, and the aqueous phase extracted with ethyl acetate (5 mL $\times$ 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , Petroleum ether: Ethyl acetate 25%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-ethyl-4-methoxy-benzonitrile (220 mg, ~70% purity) as a white solid. LCMS $[M+1]^+ = 321.9$; $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.58$ (s, 1H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 2.97 - 2.92 (m, 2H), 1.37 - 1.34 (t, $J = 6.8$ Hz 3H).

INTERMEDIATE DY



[0336] **Step 1:** A mixture of 2-bromo-5-methoxy-naphthalen-1-ol (2.60 g, 10.3 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (3.21 g, 15.4 mmol, 1.50 *eq.*), *ditert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (670 mg, 1.03 mmol, 0.10 *eq.*) and sodium carbonate (2.18 g, 20.6 mmol, 2.00 *eq.*) in dioxane (30 mL) and water (6 mL) was degassed with nitrogen then stirred at 100 °C for 0.5 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-100%) to give 5-methoxy-2-(2-methylpyrazol-3-yl)naphthalen-1-ol (720 mg, 2.83 mmol, 28% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.57 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 3.97 (s, 3H), 3.69 (s, 3H).

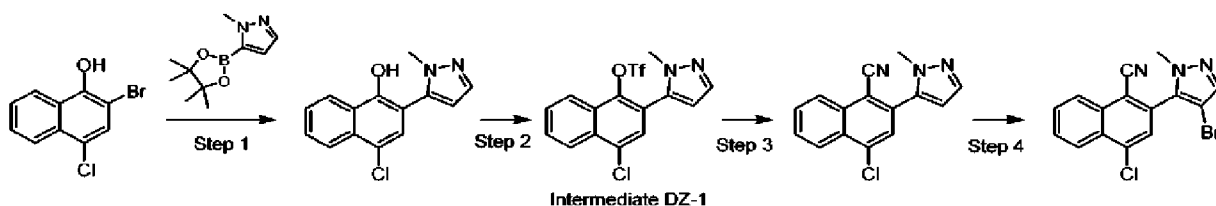
[0337] **Step 2:** To a solution of 5-methoxy-2-(2-methylpyrazol-3-yl)naphthalen-1-ol (650 mg, 2.56 mmol, 1.00 *eq.*), 4Å molecular sieves (1.00 g) and triethylamine (7.67 mmol, 1.07 mL, 3.00 *eq.*) in dichloromethane (20 mL) was added Tf₂O (3.83 mmol, 0.63 mL, 1.50 *eq.*) in a dropwise fashion at -40 °C under nitrogen. The reaction mixture was stirred at -40 °C for 0.5 hour then concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 0-15%) to give [5-methoxy-2-(2-methylpyrazol-3-yl)-1-naphthyl] trifluoromethanesulfonate (341 mg, 0.79 mmol, 30% yield) as a yellow oil. LCMS [M + 1]⁺ = 387.1; ¹H NMR (400 MHz, CDCl₃) δ = 8.40 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 4.07 (s, 3H), 3.82 (s, 3H).

[0338] **Step 3:** A mixture of [5-methoxy-2-(2-methylpyrazol-3-yl)-1-naphthyl] trifluoromethanesulfonate (290 mg, 0.67 mmol, 1.00 *eq.*), zinc cyanide (0.81 mmol, 51.1 μL, 1.20 *eq.*), Pd₂(dba)₃ (612 mg, 0.067 mmol, 0.10 *eq.*), DPPF (74 mg, 0.134 mmol, 0.20 *eq.*) and zinc powder (4.4 mg, 0.067 mmol, 0.10 *eq.*) in DMF (10 mL) was degassed with nitrogen

then stirred at 120 °C for 1 hour. The reaction mixture was then diluted with water (100 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-50%) to give 5-methoxy-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (156 mg, 0.59 mmol, 88% yield) as an off-white solid. LCMS $[M + 1]^+ = 264.1$; ¹H NMR (400 MHz, CDCl₃) δ = 8.59 (dd, J = 0.8, 8.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 8.4 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 4.07 (s, 3H), 3.89 (s, 3H).

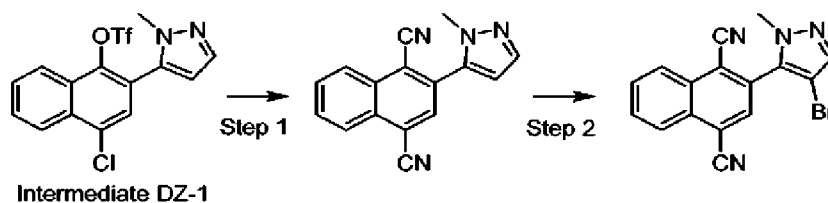
[0339] **Step 4:** To a solution of 5-methoxy-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (180 mg, 0.68 mmol, 1.00 *eq.*) in acetonitrile (2 mL) was added *N*-bromosuccinimide (146 mg, 0.82 mmol, 1.20 *eq.*). The mixture was stirred at 35 °C for 0.5 hour then concentrated under reduced pressure and the residue purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 30%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-5-methoxy-naphthalene-1-carbonitrile (174 mg, 0.51 mmol, 74% yield) as an off-white solid. LCMS $[M + 1]^+ = 342.0$; ¹H NMR (400 MHz, CDCl₃) δ = 8.64 (dd, J = 0.8, 8.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H).

INTERMEDIATE DZ



[0340] Intermediate DZ, 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-chloro-1-naphthonitrile was prepared as a yellow solid (25 mg, 0.072 mmol, 2% yield over 4 steps) starting from 2-bromo-4-chloro-naphthalen-1-ol according to the method described for the preparation of Intermediate DX. LCMS $[M+1]^+ = 347.8$; ¹H NMR (400 MHz, CDCl₃-*d*) δ = 8.48 - 8.43 (m, 1H), 8.42 - 8.38 (m, 1H), 7.91 - 7.82 (m, 2H), 7.65 (d, J = 4.4 Hz, 2H), 3.88 (s, 3H).

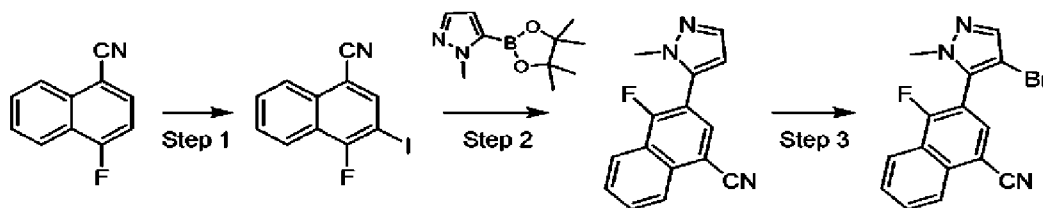
INTERMEDIATE EA



[0341] **Step 1:** A mixture of [4-chloro-2-(2-methylpyrazol-3-yl)-1-naphthyl] trifluoromethanesulfonate (38 mg, 0.097 mmol, 1.00 *eq.*), zinc cyanide (22 mg, 190 μ mol, 12.4 μ L, 2.00 *eq.*), DPPF (5.4 mg, 9.7 μ mol, 0.10 *eq.*), zinc powder (640 μ g, 9.7 μ mol, 0.10 *eq.*) and $\text{Pd}_2(\text{dba})_3$ (4.5 mg, 4.86 μ mol, 0.05 *eq.*) in DMF (1.0 mL) was degassed with nitrogen then stirred at 100 °C for 4 hours. The mixture was then concentrated and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 20%) to give 2-(2-methylpyrazol-3-yl)naphthalene-1,4-dicarbonitrile (30 mg, 93.4 μ mol, 96% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 259.0$; ^1H NMR (400 MHz, CDCl_3) δ = 8.48 - 8.44 (m, 1H), 8.44 - 8.39 (m, 1H), 7.96 (s, 1H), 7.96 - 7.94 (m, 1H), 7.94 - 7.92 (m, 1H), 7.67 (d, J = 2.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 3.92 (s, 3H).

[0342] **Step 2:** A mixture of 2-(2-methylpyrazol-3-yl)naphthalene-1,4-dicarbonitrile (30 mg, 0.093 mmol, 1.00 *eq.*), *N*-bromosuccinimide (41 mg, 0.23 mmol, 2.00 *eq.*) in acetonitrile (2.0 mL) was degassed nitrogen then stirred at 35 °C for 2 hours. The mixture was then concentrated and the residue purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 25%) to give 2-(4-bromo-2-methylpyrazol-3-yl)naphthalene-1,4-dicarbonitrile (25 mg, 0.067 mmol, 58% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 339.0$; ^1H NMR (400 MHz, CDCl_3 -*d*) δ = 8.52 - 8.41 (m, 2H), 8.01 - 7.96 (m, 2H), 7.95 (s, 1H), 7.68 (s, 1H), 3.88 (s, 3H).

INTERMEDIATE EB



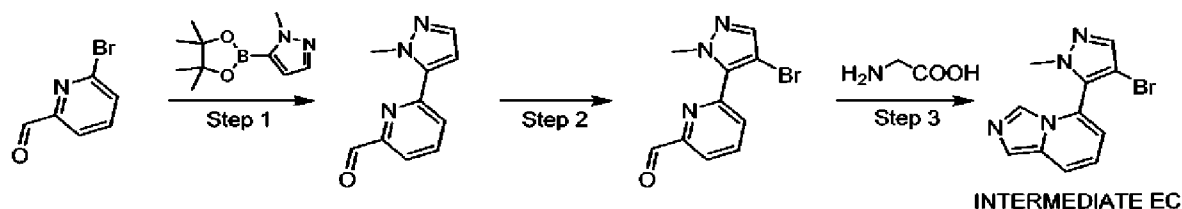
[0343] **Step 1:** A solution of *n*-butyl lithium (2.50 M, 1.87 mL, 1.00 *eq.*) was added dropwise over 30 min to a solution of 2,2,6,6-tetramethylpiperidine (660 mg, 4.67 mmol, 0.79 mL, 1.00 *eq.*) in THF (10 mL) at 0 °C and the mixture was then was cooled to -78 °C and a

solution of 4-fluoronaphthalene-1-carbonitrile (0.80 g, 4.67 mmol, 1.00 *eq.*) in THF (3 mL) was added over 15 min. The mixture was then stirred at -78 °C for 2 hours. After such time a solution of iodine (1.19 g, 4.67 mmol, 1.00 *eq.*) in THF (3 mL) was added over 30 min and the reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm-up to 25 °C and stirred for a further 12 hours. The reaction mixture was then quenched with water (50 mL) and extracted with ethyl acetate (30 mL × 2). The combine organic layers were washed with saturated sodium thiosulfate (30 mL × 3), 1 M hydrochloride (30 mL × 3) and brine (50 mL) and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (ethyl acetate: petroleum ether 0-5%) to give 4-fluoro-3-iodo-naphthalene-1-carbonitrile (1.00 g, 3.37 mmol, 72% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (d, *J* = 8.4 Hz, 1H), 8.13 - 8.07 (m, 2H), 7.72 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.68 - 7.61 (m, 1H).

[0344] **Step 2:** To a solution of 4-fluoro-3-iodo-naphthalene-1-carbonitrile (900 mg, 3.03 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.58 g, 7.57 mmol, 2.50 *eq.*) and potassium phosphate (1.29 g, 6.06 mmol, 2.00 *eq.*) in dioxane (10 mL) and water (2 mL) was added *ditert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (197 mg, 0.30 mmol, 0.10 *eq.*). The reaction was stirred at 80 °C for 18 hours under nitrogen atmosphere. The reaction mixture was then partitioned between water (20 mL) and ethyl acetate (10 mL), extracted with ethyl acetate (10 mL × 2) and the combined the organic layers dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was then purified by flash silica gel chromatography (0-25% ethyl acetate: petroleum ether gradient) to give 4-fluoro-3-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (0.80 g, 2.87 mmol, 95% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.33 - 8.25 (m, 2H), 7.91 (s, 1H), 7.88 - 7.82 (m, 1H), 7.82 - 7.75 (m, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 3.89 (d, *J* = 1.6 Hz, 3H).

[0345] **Step 3:** To a solution of 4-fluoro-3-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (200 mg, 0.80 mmol, 1.00 *eq.*) in acetonitrile (5 mL) was added 1-bromopyrrolidine-2,5-dione (212 mg, 1.19 mmol, 1.50 *eq.*) and the reaction was stirred at 25 °C for 12 hours. The reaction was then concentrated and the residue purified by flash silica gel chromatography (0-15% ethyl acetate: petroleum ether) to give 3-(4-bromo-2-methylpyrazol-3-yl)-4-fluoro-naphthalene-1-carbonitrile (0.20 g, 0.61 mmol, 76% yield) as a gray solid. LCMS [M+1]⁺ = 332.1/300.1; ¹H NMR (400 MHz, CDCl₃) δ = 8.32 (dd, *J* = 8.4, 13.1 Hz, 2H), 7.95 - 7.86 (m, 2H), 7.84 - 7.76 (m, 1H), 7.64 (s, 1H), 3.85 (d, *J* = 1.2 Hz, 3H).

INTERMEDIATE EC



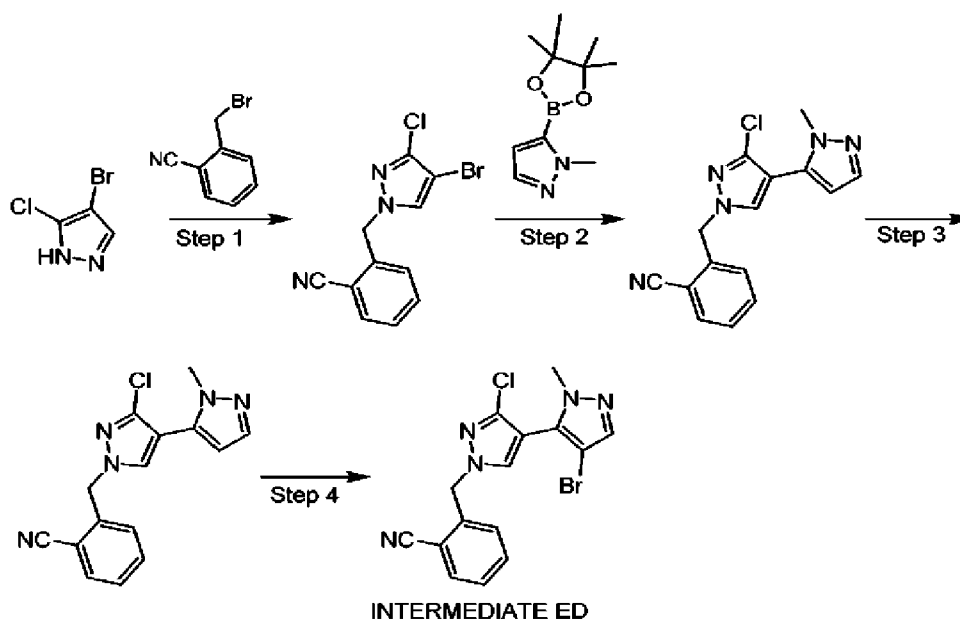
[0346] **Step 1:** To a solution of 6-bromopicolinaldehyde (1.00 g, 5.38 mmol, 1.00 *eq.*) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.12 g, 5.38 mmol, 1.00 *eq.*) in dioxane (15 mL) and water (3 mL) was added potassium carbonate (1.49 g, 10.8 mmol, 2.00 *eq.*) and Pd(dppf)Cl₂ (393 mg, 0.538 mmol, 0.10 *eq.*) at 20 °C under a nitrogen atmosphere. The mixture was then stirred at 80 °C for 6 hours. After such time the reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (50 mL × 2). The combined organic layers were washed with brine (15 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 25-50%) to give 6-(1-methyl-1*H*-pyrazol-5-yl)picolinaldehyde (800 mg, 4.27 mmol, 80% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 10.13 (d, *J* = 0.8 Hz, 1H), 7.99 - 7.89 (m, 2H), 7.83 (dd, *J* = 1.6, 7.2 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 3H).

[0347] **Step 2:** To a solution of 6-(1-methyl-1*H*-pyrazol-5-yl)picolinaldehyde (800 mg, 4.27 mmol, 1.00 *eq.*) in acetonitrile (12 mL) was added *N*-bromo-succinimide (1.14 g, 6.41 mmol, 1.50 *eq.*) at 20 °C and the mixture was stirred for 16 hours. After such time the mixture was concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 25%) to give 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)picolinaldehyde (750 mg, 2.82 mmol, 66% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 10.13 (s, 1H), 8.08 - 7.98 (m, 3H), 7.58 (s, 1H), 4.15 (s, 3H).

[0348] **Step 3:** To a solution of 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)picolinaldehyde (250 mg, 0.94 mmol, 1.00 *eq.*) in DMF (3 mL) was added 2-aminoacetic acid (78 mg, 1.03 mmol, 1.10 *eq.*), iodine (238 mg, 0.940 mmol, 0.19 mL, 1.00 *eq.*), sodium bicarbonate (158 mg, 1.88 mmol, 2.00 *eq.*) at 20 °C. The mixture was then stirred at 60 °C for 6 hours then diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by prep-TLC (SiO₂, ethyl acetate) to give 5-(4-bromo-1-

methyl-1*H*-pyrazol-5-yl)imidazo[1,5-*a*]pyridine (35 mg, 0.126 mmol, 13% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (s, 1H), 7.68 (s, 1H), 7.64 - 7.59 (m, 2H), 6.87 (dd, *J* = 6.4, 9.2 Hz, 1H), 6.66 (d, *J* = 6.4 Hz, 1H), 3.79 (s, 3H).

INTERMEDIATE ED



[0349] **Step 1:** To a solution of 4-bromo-5-chloro-1*H*-pyrazole (1.00 g, 5.51 mmol, 1.00 *eq.*) 2-(bromomethyl)benzonitrile (1.08 g, 5.51 mmol, 1.00 *eq.*) in acetonitrile (20 mL) was added potassium carbonate (914 mg, 6.61 mmol, 1.20 *eq.*) and the mixture was stirred at 80 °C for 10 hours under a nitrogen atmosphere. After such time the reaction was quenched by water (200 mL) and then extracted with ethyl acetate (150 mL × 3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the formed residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate = 10: 1) to give 2-((4-bromo-3-chloro-1*H*-pyrazol-1-yl)methyl)benzonitrile (1.00 g, 3.37 mmol, 61% yield) as a white solid. LCMS [M+1]⁺ = 297.9; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.27 (s, 1H), 7.89 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.77 - 7.68 (m, 1H), 7.61 - 7.49 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 5.52 (s, 2H).

[0350] **Step 2:** To a solution of 2-((4-bromo-3-chloro-1*H*-pyrazol-1-yl)methyl)benzonitrile (400 mg, 1.35 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (561 mg, 2.70 mmol, 2.00 *eq.*) and sodium bicarbonate (227 mg, 2.70 mmol, 2.00 *eq.*) in dioxane (10 mL) and water (1 mL) was added Pd(dppf)Cl₂ (99 mg, 0.135 mmol, 0.10

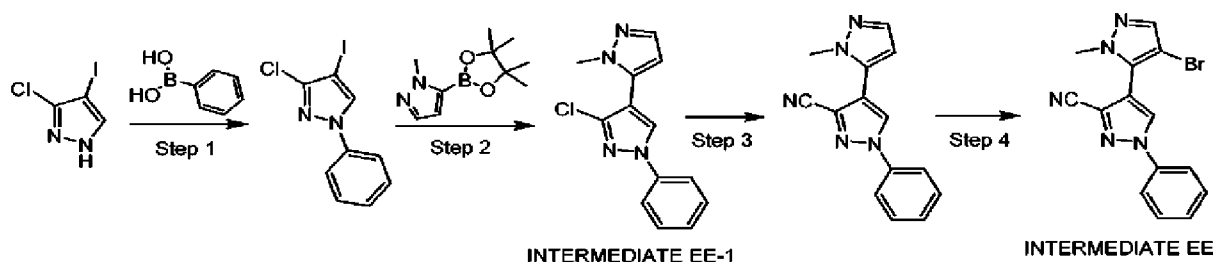
eq.) under a nitrogen atmosphere. The mixture was stirred at 110 °C for 10 hours and then the reaction was quenched by adding water (200 mL) then extracted with ethyl acetate (150 mL × 3). The combined organic phases were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 30%) to give 2-((3'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)benzonitrile (200 mg, 0.672 mmol, 50% yield) as a white solid. LCMS [M+1]⁺ = 298.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.41 (s, 1H), 7.91 (d, *J*=7.6 Hz, 1H), 7.79 - 7.70 (m, 1H), 7.62 - 7.52 (m, 1H), 7.50 - 7.42 (m, 2H), 6.42 (d, *J*=2.0 Hz, 1H), 5.58 (s, 2H), 3.81 (s, 3H).

[0351] **Step 3:** To a solution of 2-((3'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)benzonitrile (200 mg, 0.672 mmol, 1.00 *eq.*) in acetonitrile (10 mL) was added *N*-bromosuccinimide (132 mg, 0.739 mmol, 1.10 *eq.*) and the mixture was stirred at 25 °C for 10 hours under nitrogen atmosphere. After such time the reaction was quenched with water (50 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic phases was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5%) to give 2-((4-bromo-3'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)benzonitrile (130 mg, 0.345 mmol, 51% yield) as a yellow solid. LCMS [M+1]⁺ = 377.9; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37 (s, 1H), 7.92 (d, *J*=7.6 Hz, 1H), 7.83 - 7.71 (m, 1H), 7.67 (s, 1H), 7.62 - 7.55 (m, 1H), 7.45 (d, *J*=8.0 Hz, 1H), 5.61 (s, 2H), 3.73 (s, 3H).

[0352] **Step 4:** To a solution of *tert*-butyl ((4-oxo-7-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)carbamate (256 mg, 0.637 mmol, 2.00 *eq.*), 2-((4-bromo-3'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)benzonitrile (120 mg, 0.319 mmol, 1.00 *eq.*), sodium bicarbonate (54 mg, 0.637 mmol, 25 μL, 2.00 *eq.*) in water (0.5 mL) and dioxane (5.0 mL) was added Pd(dtbpf)Cl₂ (21 mg, 32 μmol, 0.10 *eq.*) under a nitrogen atmosphere and then the mixture was stirred at 110 °C for 10 hours. The reaction was then quenched with water (50 mL), extracted with ethyl acetate (40 mL × 3) and the combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 15%) to give *tert*-butyl((7-(3'-chloro-1'-(2-cyanobenzyl)-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-4-yl)-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)carbamate (115 mg, 0.201 mmol, 63% yield) as a black brown oil. LCMS [M+1]⁺ = 571.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.48 (s, 1H), 11.94 (s, 1H), 8.42 (s, 1H), 8.13 - 8.05 (m, 2H), 7.92

(d, $J=7.6$ Hz, 1H), 7.80 - 7.72 (m, 1H), 7.62 - 7.55 (m, 2H), 7.47 (d, $J=8.0$ Hz, 1H), 7.40 - 7.31 (m, 1H), 5.64 (s, 2H), 4.36 (br d, $J=5.6$ Hz, 2H), 3.74 (s, 3H), 1.38 (s, 9H).

INTERMEDIATE EE



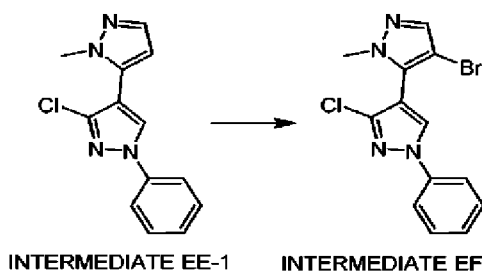
[0353] **Step 1:** To a mixture of phenylboronic acid (1.92 g, 15.8 mmol, 2.00 *eq.*) and 3-chloro-4-iodo-1*H*-pyrazole (1.80 g, 7.88 mmol, 1.00 *eq.*) in dichloromethane (30 mL) was added pyridine (1.86 g, 23.5 mmol, 1.90 mL, 2.99 *eq.*) and copper acetate (1.72 g, 9.46 mmol, 1.20 *eq.*) in one portion. The mixture was stirred at 20 °C for 16 hours, then filtered and concentrated and the residue purified by flash silica gel chromatography (0-5% ethyl acetate: petroleum ether) to give 3-chloro-4-iodo-1-phenyl-pyrazole (1.50 g, 4.93 mmol, 63% yield) as a yellow liquid. LCMS $[M+1]^+ = 305.0$; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (s, 1H), 7.63-7.59 (m, 2H), 7.49-7.43 (m, 2H), 7.36-7.30 (m, 1H).

[0354] **Step 2:** 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.23 g, 5.91 mmol, 1.50 *eq.*), 3-chloro-4-iodo-1-phenyl-pyrazole (1.20 g, 3.94 mmol, 1.00 *eq.*), potassium phosphate (1.67 g, 7.88 mmol, 2.00 *eq.*) and *ditert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (256 mg, 0.39 mmol, 0.10 *eq.*) in dioxane (20 mL) and water (4 mL) was de-gassed and then heated to 80 °C for 16 hours under a nitrogen atmosphere. The reaction mixture was then concentrated, and the residue diluted with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 3), dried over sodium sulfate, concentrated under reduced pressure and the residue purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10-15%) to give 3-chloro-4-(2-methylpyrazol-3-yl)-1-phenyl-pyrazole, Intermediate EE-1 (0.80 g, 3.09 mmol, 79% yield) as a yellow oil. LCMS $[M+1]^+ = 258.9$; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.71-7.67 (m, 2H), 7.55 (d, $J=2.0$ Hz, 1H), 7.49 (t, $J=8.0$ Hz, 2H), 7.39-7.34 (m, 1H), 6.43 (d, $J=2.0$ Hz, 1H), 3.91 (s, 3H).

[0355] **Step 3:** A mixture of 3-chloro-4-(2-methylpyrazol-3-yl)-1-phenyl-pyrazole (210 mg, 0.811 mmol, 1.00 *eq.*), tetrapotassium-hexacyanoiron(4-) trihydrate (1.03 g, 2.44 mmol, 3.00 *eq.*) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium-dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (73.6 mg, 0.081 mmol, 0.10 *eq.*) in dimethylacetamide (6 mL) and water (3 mL) was heated to 100 °C for 16 hours under nitrogen atmosphere. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-15%) to give 4-(2-methylpyrazol-3-yl)-1-phenyl-pyrazole-3-carbonitrile (200 mg, 0.80 mmol, 99% yield) as a yellow solid. LCMS $[M+1]^+ = 249.9$; ¹H NMR (400 MHz, CDCl₃) δ = 8.09 (s, 1H), 7.76-7.72 (m, 2H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.51-7.56 (m, 2H), 7.43-7.48 (m, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H).

[0356] **Step 4:** To a mixture of 4-(2-methylpyrazol-3-yl)-1-phenyl-pyrazole-3-carbonitrile (180 mg, 0.722 mmol, 1.00 *eq.*) in acetonitrile (5 mL) was added *N*-bromosuccinimide (192 mg, 1.08 mmol, 1.50 *eq.*). The mixture was stirred at 20 °C for 16 hours. The reaction mixture was then quenched with saturated sodium sulfite (15 mL), extracted with ethyl acetate (15 mL $\times$ 3), dried over anhydrous sodium sulfate, concentrated and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-20%) to give 4-(4-bromo-2-methylpyrazol-3-yl)-1-phenyl-pyrazole-3-carbonitrile (220 mg, 0.67 mmol, 93% yield) as a yellow solid. LCMS $[M+1]^+ = 327.9$; ¹H NMR (500 MHz, CDCl₃) δ = 8.17 (s, 1H), 7.78-7.74 (m, 2H), 7.59 (s, 1H), 7.58-7.54 (m, 2H), 7.49-7.45 (m, 1H), 3.95 (s, 3H).

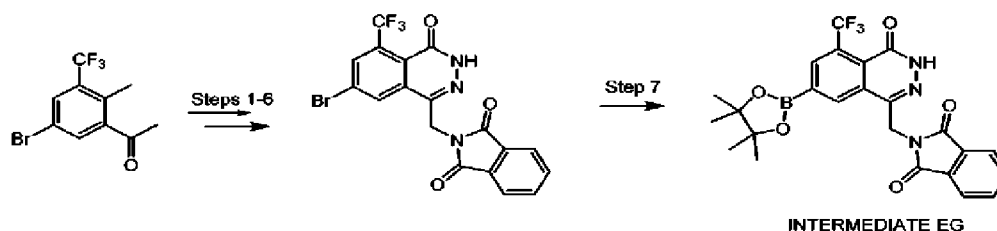
INTERMEDIATE EF



[0357] To a mixture of 3-chloro-4-(2-methylpyrazol-3-yl)-1-phenyl-pyrazole, Intermediate EE-1 (200 mg, 0.773 mmol, 1.00 *eq.*) in acetonitrile (1 mL) was added 1-bromopyrrolidine-2,5-dione (165 mg, 0.927 mmol, 1.20 *eq.*) in one portion at 20 °C. The mixture was stirred at

20 °C for 16 hours. The reaction mixture was then concentrated and the residue purified by flash silica gel chromatography (0-17% ethyl acetate: petroleum ether) to give 4-bromo-5-(3-chloro-1-phenyl-pyrazol-4-yl)-1-methyl-pyrazole (200 mg, 0.592 mmol, 77% yield) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ = 8.07 - 8.04 (m, 1H), 7.72 (dd, J = 1.2, 8.4 Hz, 2H), 7.58 (s, 1H), 7.54 - 7.49 (m, 2H), 7.42 - 7.35 (m, 1H), 3.88 (s, 3H).

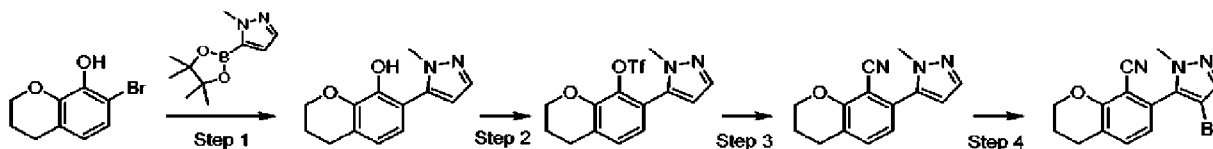
INTERMEDIATE EG



[0358] **Steps 1-6:** 2-((7-bromo-4-oxo-5-(trifluoromethyl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione was prepared as a white solid (0.50 g, 1.11 mmol, 6% yield over 6 steps) starting from 1-(5-bromo-2-methyl-3-(trifluoromethyl)phenyl)ethan-1-one following the same procedure described for the first 6 steps of Intermediate DK. LCMS $[\text{M}+1]^+ = 454.0$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 12.75 (s, 1H), 8.74 (d, J = 1.6 Hz, 1H), 8.41 (s, 1H), 7.97 - 7.92 (m, 2H), 7.91 - 7.86 (m, 2H), 5.22 (s, 2H).

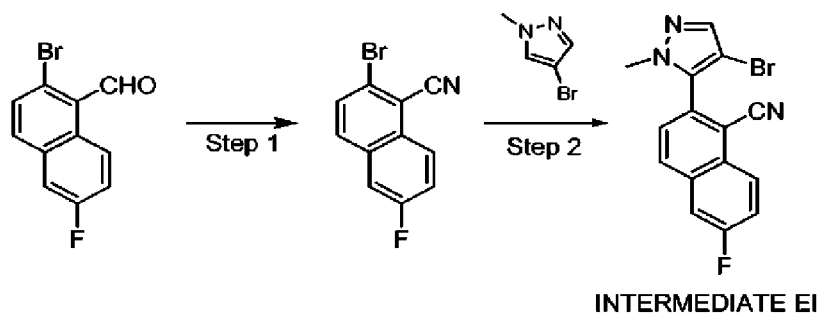
[0359] **Step 7:** A mixture of 2-((7-bromo-4-oxo-5-(trifluoromethyl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (50 mg, 0.111 mmol, 1.00 *eq.*), bis(pinacolato)diboron (34 mg, 0.133 mmol, 1.20 *eq.*), $\text{Pd}(\text{dppf})\text{Cl}_2$ (8 mg, 0.011 mmol, 0.10 *eq.*) and potassium acetate (22 mg, 0.221 mmol, 2.00 *eq.*) in dioxane (2 mL) was degassed with nitrogen and stirred at 100 °C for 1 hour. The reaction mixture was then concentrated under reduced pressure to give [4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-8-(trifluoromethyl)-2H-phthalazin-6-yl]boronic acid (46.0 mg, crude) as a brown solid. LCMS $[\text{M}-81]^+ = 418.1$.

INTERMEDIATE EH



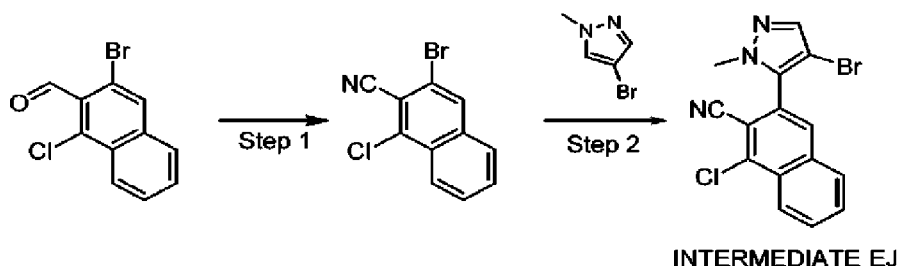
[0360] 7-(4-bromo-1-methyl-1H-pyrazol-5-yl)chromane-8-carbonitrile, Intermediate EH was prepared as a white solid (21 mg, 0.049 mmol, 84% yield) using the same 4 step procedure as used for the preparation of Intermediate DY but starting with 7-bromochroman-8-ol. LCMS $[M+1]^+ = 413.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.40$ (br s, 1H), 8.17 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.70 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 1.6$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 4.35 (br t, $J = 4.8$ Hz, 2H), 3.72 (s, 3H), 3.68 (d, $J = 2.0$ Hz, 2H), 2.89 (br t, $J = 6.0$ Hz, 2H), 2.05 - 2.00 (m, 2H).

INTERMEDIATE EI



[0361] 2-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6-fluoro-1-naphthonitrile, Intermediate EI was prepared as a white solid (60 mg, 0.182 mmol, 31% yield over 2 steps) following the same procedure as described for the preparation of Intermediate DC starting from 2-bromo-6-fluoro-1-naphthaldehyde. LCMS $[M+1]^+ = 329.8/331.8$; ^1H NMR (400MHz, $\text{CCl}_3\text{-}d$) $\delta = 8.39$ (dd, $J = 5.2, 9.2$ Hz, 1H), 8.15 (d, $J = 8.6$ Hz, 1H), 7.68 - 7.63 (m, 2H), 7.62 - 7.56 (m, 1H), 7.54 (d, $J = 8.6$ Hz, 1H), 3.86 (s, 3H).

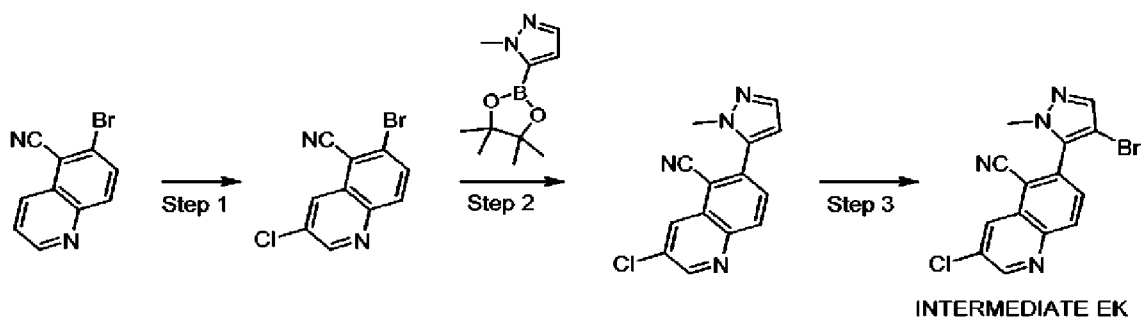
INTERMEDIATE EJ



[0362] 3-(4-bromo-1-methyl-1H-pyrazol-5-yl)-1-chloro-2-naphthonitrile, Intermediate EJ was prepared as a light yellow solid (35 mg, 0.101 mmol, 18 % yield over 2 steps) following the same procedure as described for the preparation of Intermediate DC starting from 3-

bromo-1-chloro-2-naphthaldehyde. ^1H NMR (400MHz, $\text{CCl}_3\text{-}d$) δ = 10.60 (s, 1H), 8.47 - 8.41 (m, 1H), 8.11 (s, 1H), 7.89 - 7.77 (m, 1H), 7.74 - 7.66 (m, 2H).

INTERMEDIATE EK

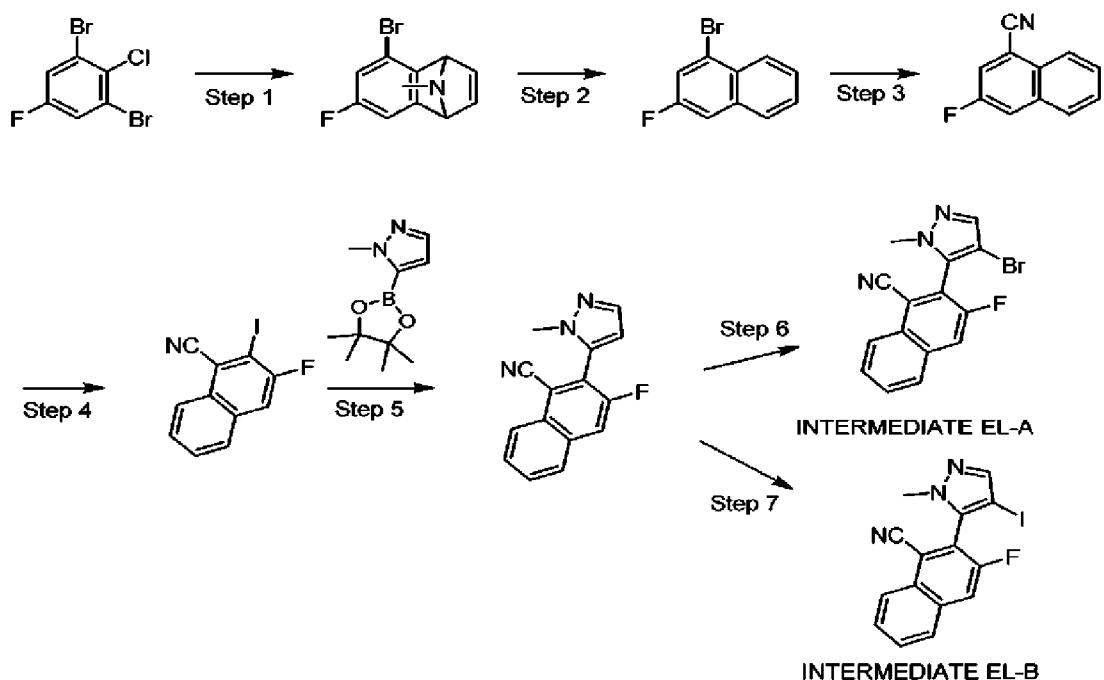


[0363] **Step 1:** To a solution of 6-bromoquinoline-5-carbonitrile (1.00 g, 4.29 mmol, 1.00 *eq.*) in acetic acid (20 mL) was added *N*-chlorosuccinimide (5.73 g, 42.9 mmol, 10.0 *eq.*). The mixture was stirred at 135 °C for 24 hours. The pH of the reaction mixture was then adjusted to pH 7 with 2 *N* sodium hydroxide aqueous solution (5 mL), diluted with water (50 mL) and extracted with dichloromethane (30 mL $\times$ 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10-15%) to give 6-bromo-3-chloro-quinoline-5-carbonitrile (512 mg, 1.91 mmol, 45% yield) as an off-white solid. LCMS $[\text{M} + 1]^+ = 269.0$; ^1H NMR (400 MHz, CDCl_3) δ = 8.94 (s, 1H), 8.49 (dd, J = 0.8, 2.4 Hz, 1H), 8.18 (s, 1H), 7.93 (d, J = 9.2 Hz, 1H).

[0364] **Step 2:** A mixture of 6-bromo-3-chloro-quinoline-5-carbonitrile (512 mg, 1.91 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (398 mg, 1.91 mmol, 1.00 *eq.*), *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (125 mg, 0.19 mmol, 0.10 *eq.*), sodium bicarbonate (322 mg, 3.83 mmol, 0.15 mL, 2.00 *eq.*) in dioxane (10 mL) and water (2 mL) was degassed with nitrogen and stirred at 80 °C for 0.5 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 30%) to give 3-chloro-6-(2-methylpyrazol-3-yl)quinoline-5-carbonitrile (250 mg, 0.930 mmol, 49% yield) as a yellow solid. LCMS $[\text{M} + 1]^+ = 269.1$; ^1H NMR (400 MHz, CDCl_3) δ = 9.00 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.42 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 6.63 (d, J = 1.6 Hz, 1H), 3.92 (s, 3H).

[0365] **Step 3:** To a solution of 3-chloro-6-(2-methylpyrazol-3-yl)quinoline-5-carbonitrile (249 mg, 0.927 mmol, 1.00 *eq.*) in acetonitrile (5 mL) was added *N*-bromosuccinimide (214 mg, 1.20 mmol, 1.30 *eq.*). The mixture was stirred at 35 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-15%) to give 6-(4-bromo-2-methylpyrazol-3-yl)-3-chloro-quinoline-5-carbonitrile (289 mg, 0.831 mmol, 90% yield) as a yellow solid. LCMS $[M + 1]^+ = 349.0$; ¹H NMR (400 MHz, CDCl₃) δ = 9.04 (d, *J* = 2.4 Hz, 1H), 8.64 (dd, *J* = 0.8, 2.4 Hz, 1H), 8.49 - 8.46 (m, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.67 (s, 1H), 3.87 (s, 3H).

INTERMEDIATES EL-A and EL-B



[0366] **Step 1:** To a solution of 1,3-dibromo-2-chloro-5-fluoro-benzene (61.0 g, 212 mmol, 1.00 *eq.*) and 1-methylpyrrole (34.3 g, 423 mmol, 37.7 mL, 2.00 *eq.*) in toluene (1500 mL) was added *n*-butyl lithium (2.50 M in THF, 88.9 mL, 1.05 *eq.*) dropwise at -30 °C under nitrogen. The mixture was then stirred at -30 °C for 0.5 hour then allowed to warm to 25 °C and stirred for 12 hours. After such time the reaction mixture was quenched with water (20 mL) and concentrated under reduced pressure to give a residue. The residue was diluted with ethyl acetate (1000 mL), washed with brine (1000 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂,

petroleum ether: ethyl acetate 10-50%) to give 3-bromo-5-fluoro-11-methyl-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (30.0 g, 118 mmol, 56% yield) as a brown liquid. ¹H NMR (400 MHz, CDCl₃) δ = 7.10 - 6.65 (m, 4H), 4.83 - 4.44 (m, 2H), 2.31 - 2.09 (m, 3H).

[0367] **Step 2:** To a solution of 3-bromo-5-fluoro-11-methyl-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (61.5 g, 242 mmol, 1.00 *eq.*) in chloroform (1300 mL) was carefully added *m*-CPBA (98.2 g, 484 mmol, 85% purity, 2.00 *eq.*) in portions maintaining the inner temperature below 40 °C. After 2 hours, the brown solution turned yellow and the mixture was stirred at 25°C for a further 24 hours. After such time the mixture was diluted with dichloromethane (1000 mL) and washed with saturated sodium sulfite (1500 mL × 2) followed by brine (1500 mL), then dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 0-10%) to give 1-bromo-3-fluoro-naphthalene (37.8 g, 168 mmol, 70 % yield) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ = 8.25 - 8.18 (m, 1H), 7.75 (br d, *J* = 3.2 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.0 Hz, 1H), 7.58 - 7.52 (m, 2H), 7.47 - 7.40 (m, 1H).

[0368] **Step 3:** A mixture of 1-bromo-3-fluoro-naphthalene (34.8 g, 155 mmol, 1.00 *eq.*), Pd₂(dba)₃ (14.2g, 15.5 mmol, 0.10 *eq.*), zinc cyanide (45.4 g, 387 mmol, 24.5 mL, 2.50 *eq.*), DPPF (17.1 g, 30.9 mmol, 0.20 *eq.*) and Zn power (1.01 g, 15.5 mmol, 0.10 *eq.*) in DMF (400 mL) was degassed with nitrogen and then the mixture was stirred at 115 °C for 4 hours. After such time the mixture was filtered, diluted with ethyl acetate (1000 mL), washed with brine (1000 mL × 2), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 0-10%) to give 3-fluoronaphthalene-1-carbonitrile (21.5 g, 126 mmol, 81% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.26 - 8.21 (m, 1H), 7.92 - 7.85 (m, 1H), 7.76 - 7.65 (m, 4H).

[0369] **Step 4:** *n*-butyl lithium (2.50 M in hexane, 2.83 mL, 1.10 *eq.*) was added to a solution of *N*-isopropylpropan-2-amine (845 mg, 8.35 mmol, 1.18 mL, 1.30 *eq.*) in THF (15 mL) at -70 °C and the reaction mixture was stirred at -70 °C for 15 minutes and then 3-fluoronaphthalene-1-carbonitrile (1.10 g, 6.43 mmol, 1.00 *eq.*) in THF (2 mL) was added to the mixture and the reaction mixture was stirred for 30 minutes at -70 °C. A solution of iodine (2.12 g, 8.35 mmol, 1.30 *eq.*) in THF (2.00 mL) was then added to the reaction mixture at -70 °C and the solution was stirred at -70 °C for a further 30 minutes and then the mixture was warmed to 25 °C and stirred at 25 °C for 10 hours. After such time the reaction was quenched

with water (100 mL), and diluted with ethyl acetate (250 mL), washed with saturated sodium thiosulfate (100 mL $\times$ 2) and brine (250 mL). The organic phase was dried over anhydrous sodium sulfate filtered, concentrated and the formed residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 0-15%) to give 3-fluoro-2-iodo-naphthalene-1-carbonitrile (1.70 g, 5.72 mmol, 89% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.36 - 8.24 (m, 1H), 7.83 - 7.71 (m, 1H), 7.59 - 7.48 (m, 3H).

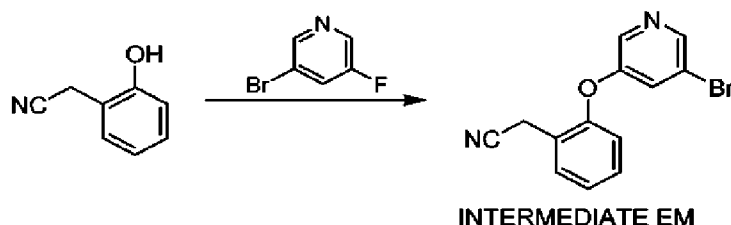
[0370] **Step 5:** A mixture of 3-fluoro-2-iodo-naphthalene-1-carbonitrile (800 mg, 2.69 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.23 g, 5.92 mmol, 2.20 *eq.*), Pd(dtbpf)Cl₂ (176 mg, 0.269 mmol, 0.10 *eq.*), sodium bicarbonate (679 mg, 8.08 mmol, 3.00 *eq.*) in dioxane (10 mL) and water (2 mL) was degassed with nitrogen and stirred at 80 °C for 12 hours. After such time the mixture was concentrated and the residue purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5-50%) to give 3-fluoro-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (500 mg, 1.99 mmol, 74% yield) as a yellow solid. LCMS [M+1]⁺ = 252.1; ¹H NMR (400 MHz, CDCl₃) δ = 8.35 - 8.27 (m, 1H), 8.00 - 7.92 (m, 1H), 7.87 (d, *J* = 9.6 Hz, 1H), 7.79 - 7.70 (m, 2H), 7.68 (d, *J* = 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 3.85 (d, *J* = 1.2 Hz, 3H).

[0371] **Step 6:** To a solution of 3-fluoro-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (500 mg, 1.99 mmol, 1.00 *eq.*) in acetonitrile (8 mL) was added *N*-bromosuccinimide (638 mg, 3.58 mmol, 1.80 *eq.*). The mixture was stirred at 25 °C for 3 hours. After such time the mixture was concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10-50%) to give 2-(4-bromo-2-methylpyrazol-3-yl)-3-fluoro-naphthalene-1-carbonitrile (550 mg, 1.56 mmol, 78% yield) as a yellow solid. LCMS [M+1]⁺ = 331.9; ¹H NMR (400 MHz, CDCl₃) δ = 8.40 - 8.31 (m, 1H), 8.01 - 7.95 (m, 1H), 7.91 (d, *J* = 9.6 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.68 (s, 1H), 3.84 (s, 3H).

[0372] **Step 7:** To a solution of 3-fluoro-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (20.0 g, 79.6 mmol, 1.00 *eq.*) in acetonitrile (300 mL) was added *N*-iodosuccinimide (89.5 g, 398 mmol, 5.00 *eq.*). The mixture was stirred at 80 °C for 12 hours. After such time the mixture was concentrated and the residue was triturated with methyl alcohol (100 mL) at 25 °C for 30 min and the mixture filtered and dried to give 3-fluoro-2-(4-iodo-2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (25.2 g, 66.8 mmol, 84% yield) as a yellow solid. LCMS [M+1]⁺ = 378.0; ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (br d, *J* = 8.4 Hz,

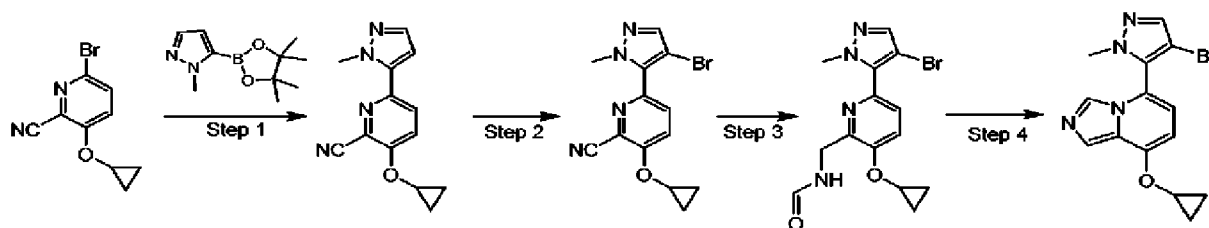
1H), 7.98 (br d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 9.2$ Hz, 1H), 7.82 - 7.74 (m, 2H), 7.74 - 7.67 (m, 1H), 3.92 - 3.82 (m, 3H).

INTERMEDIATE EM



[0373] A mixture of 2-(2-hydroxyphenyl)acetonitrile (182 mg, 1.36 mmol, 1.20 *eq.*), 3-bromo-5-fluoro-pyridine (200 mg, 1.14 mmol, 1.00 *eq.*), potassium carbonate (393 mg, 2.84 mmol, 2.50 *eq.*) in DMF (10 mL) was stirred at 75 °C for 3 hours under a nitrogen atmosphere. The mixture was concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 15%) to give 2-[2-[(5-bromo-3-pyridyl)oxy]phenyl]acetonitrile (200 mg, 0.43 mmol, 38% yield) as a yellow oil. LCMS $[M+1]^+ = 289.0$.

INTERMEDIATE EN



[0374] **Step 1:** To a solution of 6-bromo-3-cyclopropoxypicolinonitrile (800 mg, 3.35 mmol, 1.00 *eq.*) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (732 mg, 3.51 mmol, 1.05 *eq.*) in dioxane (20 mL) and water (0.4 mL) was added *di*-tert-butyl(cyclopentyl)phosphane-dichloropalladium-iron (218 mg, 0.335 mmol, 0.10 *eq.*) and sodium carbonate (709 mg, 6.69 mmol, 2.00 *eq.*) at 25 °C. The mixture was degassed and purged with nitrogen for 3 times, and then stirred at 80 °C for 2 hours. After such time the reaction mixture was quenched with water (20 mL) and then extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by flash silica gel chromatography (SiO₂, petroleum ether: ethyl acetate 0-10%) to give 3-cyclopropoxy-6-(1-

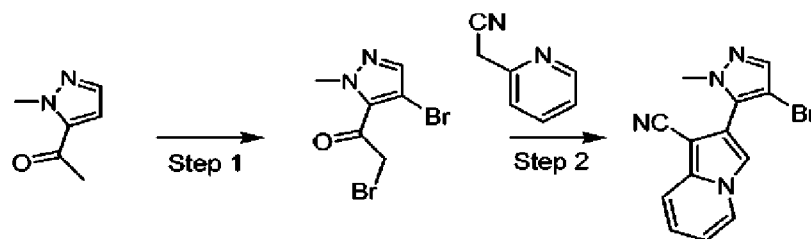
methyl-1*H*-pyrazol-5-yl)picolinonitrile (750 mg, 2.97 mmol, 89% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ = 7.77 (s, 2H), 7.51 (d, *J* = 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 4.22 (s, 3H), 3.96 - 3.91 (m, 1H), 0.98 - 0.92 (m, 4H).

[0375] **Step 2:** To a solution of 3-cyclopropoxy-6-(1-methyl-1*H*-pyrazol-5-yl)picolinonitrile (650 mg, 2.71 mmol, 1.00 *eq.*) in acetonitrile (20 mL) was added *N*-bromosuccinimide (723 mg, 4.06 mmol, 1.50 *eq.*) at 0 °C and the mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate = 1: 1) to give 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypicolinonitrile (1.1 g, crude) as a yellow solid. LCMS [M+1] = 318.9/320.9; ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.52 (s, 1H), 4.05 (s, 3H), 3.99 - 3.92 (m, 1H), 0.99 - 0.92 (m, 4H).

[0376] **Step 3:** To a solution of 6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypicolinonitrile (300 mg, 0.94 mmol, 1.00 *eq.*) in THF (20 mL) was added DIBAL-H (1.00 M, 5.64 mL, 6.00 *eq.*) at 25 °C and the mixture was stirred at 25 °C for 3 hours. After such time the reaction was quenched by the addition of sodium thiosulfate solution (20 mL). The mixture was extracted with ethyl acetate (30 mL $\times$ 3) and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 1: 1) to give (6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypyridin-2-yl) methanamine (160 mg, 0.495 mmol) as a yellow solid. A mixture of (6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypyridin-2-yl) methanamine (160 mg, 0.495 mmol, 1.00 *eq.*) in ethyl formate (3 mL) was stirred at 25 °C for 2 hours followed by the addition of water (2 mL). The mixture was then extracted with ethyl acetate (3 mL $\times$ 3) and the combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 0-10%) to give N-((6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypyridin-2-yl) methyl) formamide (140 mg, 0.359 mmol, 73% yield) as a yellow solid. LCMS [M+1]⁺ = 351.0/353.0; ¹H NMR (400 MHz, CDCl₃) δ = 8.36 (s, 1H), 7.68 - 7.61 (m, 2H), 7.55 - 7.52 (m, 1H), 7.03 (br s, 1H), 4.62 (d, *J* = 4.4 Hz, 2H), 3.99 (s, 3H), 3.85 (tt, *J* = 3.2, 5.6 Hz, 1H), 0.92 - 0.85 (m, 4H).

[0377] **Step 4:** To a solution of *N*-((6-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-cyclopropoxypyridin-2-yl) methyl) formamide (140 mg, 0.359 mmol, 1.00 *eq*) and diisopropylethylamine (104 mg, 0.80 mmol, 0.14 mL, 2.00 *eq*.) in dichloromethane (8 mL) was added Tf₂O (225 mg, 0.078 mmol, 0.13 mL, 2.00 *eq*.) at -40 °C then allowed to warm to ambient temperature and stirred at 25 °C for 6 hours. After such time water (2 mL) was added and the mixture extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 0-10%) to give 5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-8-cyclopropoxyimidazo[1,5-*a*]pyridine (110 mg, 0.314 mmol, 79% yield) as a yellow solid. LCMS [M+1]⁺ = 332.9/334.9; ¹H NMR (400 MHz, CDCl₃) δ = 7.72 - 7.60 (m, 3H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 7.4 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.77 (s, 3H), 0.98 - 0.87 (m, 4H).

INTERMEDIATE EO

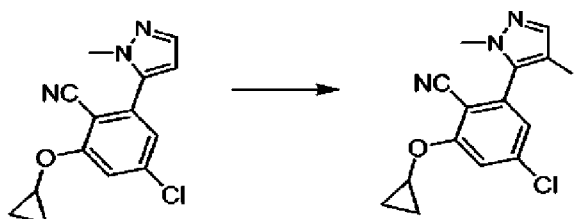


[0378] **Step 1:** To a solution of 1-(2-methylpyrazol-3-yl)ethanone (400 mg, 3.22 mmol, 1.00 *eq*.) in THF (6 mL) was added 1-bromopyrrolidine-2,5-dione (1.43 g, 8.06 mmol, 2.50 *eq*.) and the mixture was stirred at 25 °C for 12 hours. After such time the reaction mixture was concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 20%) to give 2-bromo-1-(4-bromo-2-methyl-pyrazol-3-yl)ethanone (800 mg, 2.84 mmol, 88% yield) as a yellow oil. LCMS [M+1]⁺ = 282.9; ¹H NMR (400 MHz, CDCl₃) δ = 7.54 (s, 1H), 4.62 (s, 2H), 4.16 (s, 3H).

[0379] **Step 2:** A solution of 2-bromo-1-(4-bromo-2-methyl-pyrazol-3-yl)ethanone (400 mg, 1.42 mmol, 1.00 *eq*.) and 2-(2-pyridyl)acetonitrile (335 mg, 2.84 mmol, 0.31 mL, 2.00 *eq*.) in acetonitrile (6 mL) was stirred at 70 °C for 11 hours followed by the addition of triethylamine (431 mg, 4.26 mmol, 0.59 mL, 3.00 *eq*.) and stirred at 70 °C for a further 1 hour. The reaction mixture was then concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 30%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)indolizine-1-carbonitrile (100 mg, 0.332 mmol, 23% yield) as a yellow solid. LCMS [M+1]⁺ = 301.0; ¹H

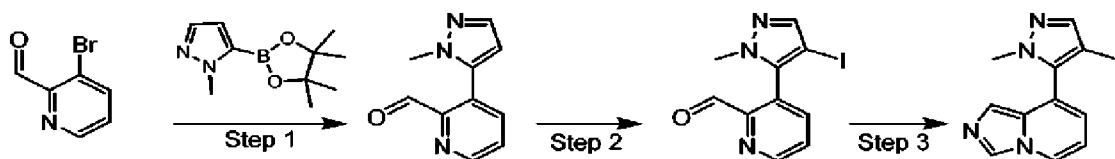
NMR (400 MHz, CDCl₃) δ = 8.10 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.59 (s, 1H), 7.44 (s, 1H), 7.22 - 7.15 (m, 1H), 6.89 (t, J = 6.4 Hz, 1H), 3.96 (s, 3H).

INTERMEDIATE EP



[0380] To a solution of 4-chloro-2-(cyclopropoxy)-6-(2-methylpyrazol-3-yl)benzonitrile (150 mg, 0.55 mmol, 1.00 *eq.*) in acetic acid (1.0 mL) was added *N*-iodosuccinimide (247 mg, 1.10 mmol, 2.00 *eq.*) and the mixture was stirred at 25 °C for 1 hour. The reaction mixture was then diluted with ethyl acetate (30 mL) and washed with brine (30 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 20%) to give 4-chloro-2-(cyclopropoxy)-6-(4-iodo-2-methylpyrazol-3-yl)benzonitrile (135 mg, 0.33 mmol, 61% yield) as a yellow solid. LCMS $[M + H]^+$ = 399.9; ¹H NMR (400 MHz, CDCl₃) δ = 7.53 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 3.90 - 3.79 (m, 1H), 3.75 (s, 3H), 0.99 - 0.76 (m, 4H).

INTERMEDIATE EQ



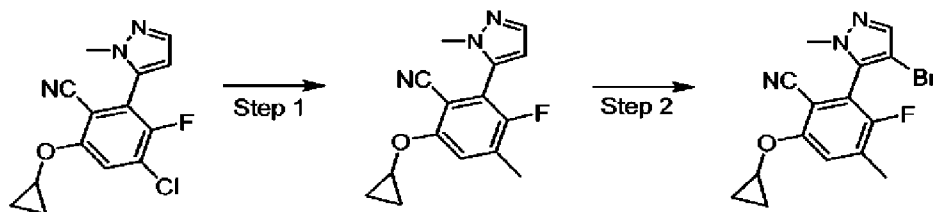
[0381] **Step 1:** A mixture of 3-bromopyridine-2-carbaldehyde (1.00 g, 5.38 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.12 g, 5.38 mmol, 1.00 *eq.*), sodium bicarbonate (1.13 g, 13.4 mmol, 0.52 mL, 2.50 *eq.*) and triphenyl phosphine (141 mg, 0.54 mmol, 0.10 *eq.*) in DMF (10 mL) and water (2 mL) was degassed and purged with nitrogen 3 times, then palladium acetate (60 mg, 0.27 mmol, 0.05 *eq.*) was added to the mixture and stirred at 80 °C for 16 hours. After such time the reaction solution was filtered, poured into water (2 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether:

ethyl acetate 20-100%) to give 3-(2-methylpyrazol-3-yl)pyridine-2-carbaldehyde (637 mg, 3.40 mmol, 63% yield) as a brown solid. LCMS $[M+1]^+ = 188.0$; ^1H NMR (400 MHz, CDCl_3) $\delta = 10.14 - 10.06$ (m, 1H), 8.93 (dd, $J = 1.6, 4.8$ Hz, 1H), 7.79 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.64 - 7.58 (m, 2H), 6.30 (d, $J = 2.0$ Hz, 1H), 3.67 (s, 3H).

[0382] **Step 2:** To a solution of 3-(2-methylpyrazol-3-yl)pyridine-2-carbaldehyde (200 mg, 1.07 mmol, 1.00 *eq.*) in acetonitrile (5 mL) was added *N*-iodosuccinimide (480 mg, 2.14 mmol, 2.00 *eq.*) and the mixture was stirred at 20 °C for 16 hours. The reaction was diluted by ethyl acetate (35 mL), washed with saturated sodium thiosulfate (5 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 20-100%) to give 3-(4-iodo-2-methylpyrazol-3-yl)pyridine-2-carbaldehyde (290 mg, 0.93 mmol, 87% yield) as a white solid. LCMS $[M+1]^+ = 313.8$; ^1H NMR (400 MHz, CDCl_3) $\delta = 10.07$ (s, 1H), 8.97 (dd, $J = 1.6, 4.8$ Hz, 1H), 7.79 - 7.73 (m, 1H), 7.68 (dd, $J = 4.8, 7.6$ Hz, 1H), 7.63 (s, 1H), 3.69 (s, 3H).

[0383] **Step 3:** To a solution of 3-(4-iodo-2-methylpyrazol-3-yl)pyridine-2-carbaldehyde (290 mg, 0.93 mmol, 1.00 *eq.*) in DMF (5 mL) was added 2-aminoacetic acid (77 mg, 1.02 mmol, 1.10 *eq.*), iodine (235 mg, 0.93 mmol, 0.18 mL, 1.00 *eq.*) and sodium bicarbonate (155 mg, 1.85 mmol, 2.00 *eq.*). Then the mixture was then stirred at 60 °C for 6 hours. The reaction mixture was diluted with ethyl acetate (35 mL), washed with saturated sodium thiosulfate solution (2 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 20-100%) to give 8-(4-iodo-2-methylpyrazol-3-yl)imidazo[1,5-a]pyridine (100 mg, 0.31 mmol, 33% yield) as a yellow gum. LCMS $[M-1]^- = 324.9$; ^1H NMR (400 MHz, CDCl_3) $\delta = 8.24$ (s, 1H), 8.05 (d, $J = 6.4$ Hz, 1H), 7.65 (s, 1H), 7.19 (s, 1H), 6.78 - 6.69 (m, 2H), 3.82 (s, 3H).

INTERMEDIATE ER

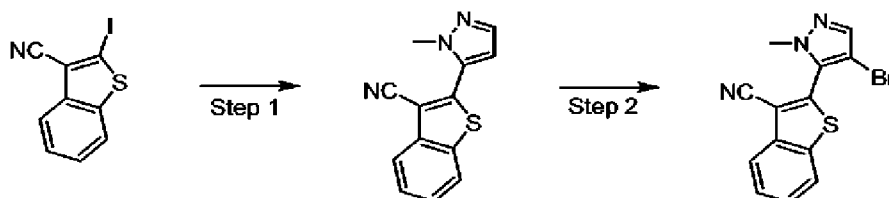


[0384] **Step 1:** A mixture of 4-chloro-6-(cyclopropoxy)-3-fluoro-2-(2-methylpyrazol-3-yl)benzonitrile (200 mg, 0.69 mmol, 1.00 *eq.*), methylboronic acid (205 mg, 3.43 mmol, 5.00

eq.), *ditert*-butyl(cyclopentyl)phosphane-dichloropalladium-iron (45 mg, 0.069 mmol, 0.10 *eq.*) and potassium carbonate (284 mg, 2.06 mmol, 3.00 *eq.*) in dioxane (2 mL) was degassed, purged with nitrogen 3 times and stirred at 100 °C for 2 hours. The mixture was then concentrated and purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 25%) to give 6-(cyclopropoxy)-3-fluoro-4-methyl-2-(2-methylpyrazol-3-yl)benzonitrile (35 mg, 0.10 mmol, 15% yield) as a yellow oil. LCMS $[M+1]^+ = 274.3$; ¹H NMR (400 MHz, CDCl₃) $\delta = 7.60$ (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 6.0$ Hz, 1H), 6.46 (d, $J = 2.0$ Hz, 1H), 3.86 (td, $J = 2.8, 5.6$ Hz, 1H), 3.80 (s, 3H), 2.43 (d, $J = 2.0$ Hz, 3H), 0.93 - 0.88 (m, 4H).

[0385] **Step 2:** A mixture of 6-(cyclopropoxy)-3-fluoro-4-methyl-2-(2-methylpyrazol-3-yl)benzonitrile (35 mg, 0.13 mmol, 1.00 *eq.*), *N*-bromosuccinimide (46 mg, 0.26 mmol, 2.00 *eq.*) in acetonitrile (3 mL) was stirred at 40 °C for 2 hours under a nitrogen atmosphere. The mixture was then concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 25%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-3-fluoro-4-methyl-benzonitrile (25 mg, 0.040 mmol, 31% yield) as a white solid. LCMS $[M+1]^+ = 352.0$; ¹H NMR (400 MHz, CDCl₃) $\delta = 7.59$ (d, $J = 2.8$ Hz, 1H), 7.31 (br d, $J = 2.8$ Hz, 1H), 3.90 - 3.83 (m, 1H), 3.78 (d, $J = 2.8$ Hz, 3H), 2.44 (br s, 3H), 0.92 (br dd, $J = 3.2, 6.4$ Hz, 4H).

INTERMEDIATE ES

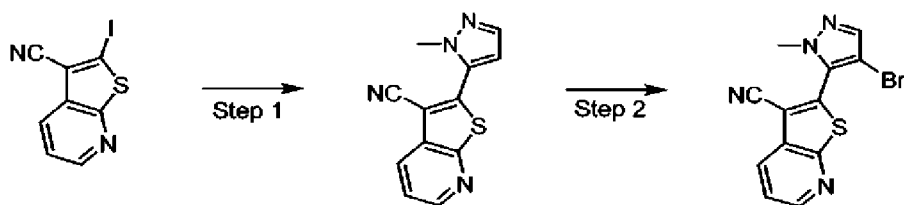


[0386] **Step 1:** To a mixture of 2-iodobenzothiophene-3-carbonitrile (280 mg, 0.98 mmol, 1.00 *eq.*), sodium carbonate (312 mg, 2.95 mmol, 3.00 *eq.*) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (409 mg, 1.96 mmol, 2.00 *eq.*) in dioxane (4 mL) and water (1 mL) was added *ditert*-butyl(cyclopentyl)phosphane-dichloropalladium-iron (64 mg, 0.098 mmol, 0.10 *eq.*) and sodium carbonate (312 mg, 2.95 mmol, 3.00 *eq.*) and the mixture was stirred at 80 °C for 2 hours. After such time water (5 mL) was added and the mixture extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phase were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 10%) to give 2-(2-

methylpyrazol-3-yl)benzothiophene-3-carbonitrile (150 mg, 64% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 8.06 - 8.01 (m, 1H), 7.94 - 7.89 (m, 1H), 7.64 - 7.61 (m, 1H), 7.61 - 7.51 (m, 2H), 6.79 (d, $J = 1.6$ Hz, 1H), 4.09 (s, 3H).

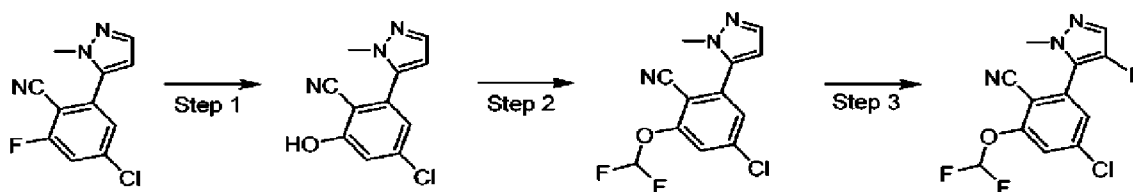
[0387] **Step 2:** To a mixture of 2-(2-methylpyrazol-3-yl)benzothiophene-3-carbonitrile (150 mg, 0.63 mmol, 1.00 eq.) in acetonitrile (2 mL) was added *N*-bromosuccinimide (112 mg, 0.63 mmol, 1.00 eq.) and the mixture was stirred at 25 °C for 12 hours. After such time the reaction mixture was added to a saturated sodium bicarbonate solution (5 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 0-100%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)benzothiophene-3-carbonitrile (160 mg, 75% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 319.9$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 8.10 - 8.05 (m, 1H), 7.98 - 7.93 (m, 1H), 7.65 (s, 1H), 7.63 - 7.56 (m, 2H), 3.98 (s, 3H).

INTERMEDIATE ET



[0388] Intermediate ES, 2-(4-bromo-2-methyl-pyrazol-3-yl)thieno[2,3-*b*]pyridine-3-carbonitrile, was prepared as a yellow solid (80.0 mg, 0.25 mmol, 22% yield over 2 steps) from thieno[2,3-*b*]pyridine-3-carbonitrile in steps following the procedure described for Intermediate ER. LCMS $[\text{M}+1]^+ = 320.9$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 8.78 (dd, $J = 1.6, 4.4$ Hz, 1H), 8.34 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.66 (s, 1H), 7.58 (dd, $J = 4.4, 8.0$ Hz, 1H), 3.99 (s, 3H).

INTERMEDIATE EU

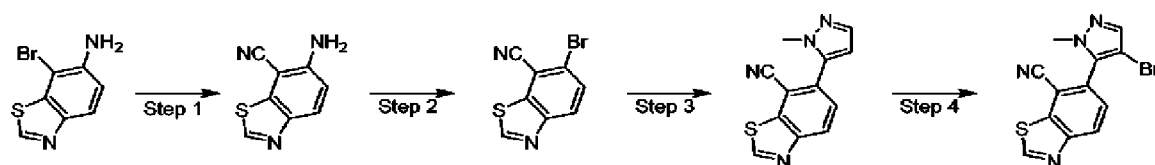


[0389] **Step 1:** To a solution of 2-methylsulfonylethanol (569 mg, 4.58 mmol, 1.20 *eq.*) in DMF (30 mL) was added sodium hydride (183 mg, 4.58 mmol, 60.0% purity, 1.20 *eq.*) at 0 °C. After stirring for 0.5 hour 4-chloro-2-fluoro-6-(2-methylpyrazol-3-yl)benzonitrile (900 mg, 3.82 mmol, 1.00 *eq.*) in DMF (5 mL) was added in a dropwise fashion at 0 °C. The reaction mixture was stirred at 25 °C for 1 hour. After such time the mixture was diluted with water (100 mL), extracted with ethyl acetate (100 mL × 3), the aqueous phase adjusted to pH 1 with HCl (10 mL) and further extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give 4-chloro-2-hydroxy-6-(2-methylpyrazol-3-yl)benzonitrile (455 mg, crude) as a yellow solid which used into the next step without further purification. LCMS $[M]^+ = 234.1$; $^1\text{H NMR}$ (400 MHz, DMSO-*d*₆) $\delta = 11.96$ (br s, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 2.0$ Hz, 1H), 6.50 (d, $J = 2.0$ Hz, 1H), 3.76 (s, 3H).

[0390] **Step 2:** To a solution of 4-chloro-2-hydroxy-6-(2-methylpyrazol-3-yl)benzonitrile (150 mg, 0.642 mmol, 1.00 *eq.*) and sodium 2-chloro-2,2-difluoro-acetate (392 mg, 2.57 mmol, 4.00 *eq.*) in DMF (2 mL) and water (0.2 mL) was added cesium carbonate (314 mg, 0.96 mmol, 1.50 *eq.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was then quenched by addition water (40 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 25%) to give 4-chloro-2-(difluoromethoxy)-6-(2-methylpyrazol-3-yl)benzonitrile (85 mg, 0.30 mmol, 47% yield) as a yellow solid. LCMS $[M]^+ = 284.0$; $^1\text{H NMR}$ (400 MHz, DMSO-*d*₆) δ (ppm) = 7.76 (s, 1H), 7.74 (d, $J = 2.0$ Hz, 1H), 7.72 - 7.71 (m, 1H), 7.58 (d, $J = 2.0$ Hz, 1H), 7.54 (s, 1H), 7.36 (s, 1H), 6.60 (d, $J = 2.0$ Hz, 1H), 3.80 (s, 3H).

[0391] **Step 3:** To a solution of 4-chloro-2-(difluoromethoxy)-6-(2-methylpyrazol-3-yl)benzonitrile (85 mg, 0.30 mmol, 1.00 *eq.*) in acetic acid (2 mL) was added *N*-iodide succinimide (135 mg, 0.60 mmol, 2.00 *eq.*). The mixture was stirred at 25 °C for 1 hour then the reaction mixture was quenched by addition of water (40 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 20%) to give 4-chloro-2-(difluoromethoxy)-6-(4-iodo-2-methyl-pyrazol-3-yl) benzonitrile (90 mg, 0.22 mmol, 73% yield) as a yellow solid. LCMS $[M + H]^+ = 409.9$; $^1\text{H NMR}$ (400 MHz, CD₃OD-*d*₄) δ (ppm) = 7.72 - 7.68 (m, 1H), 7.67 (s, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.42 - 7.02 (m, 1H), 3.83 (s, 3H).

INTERMEDIATE EV



[0392] **Step 1:** A mixture of 7-bromo-1,3-benzothiazol-6-amine (2.00 g, 8.73 mmol, 1.00 eq.), zinc cyanide (1.54 g, 13.1 mmol, 1.50 eq.), $\text{Pd}_2(\text{dba})_3$ (80 mg, 0.87 mmol, 0.01 eq.), DPPF (97 mg, 0.175 mmol, 0.02 eq.) and zinc powder (5.7 mg, 0.087 mmol, 0.01 eq.) in DMF (20 mL) was degassed, purged with nitrogen 3 times, and then stirred at 140 °C for 16 hours. After such time the reaction mixture was extracted with ethyl acetate 150 mL (50 mL $\times$ 3) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the formed residue purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10-25%) to give 6-amino-1,3-benzothiazole-7-carbonitrile (1.05 g, 4.66 mmol, 53% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 176.1$; ^1H NMR (400 MHz, CDCl_3 -d) $\delta = 8.79$ (s, 1H), 8.05 (d, $J = 8.8$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 4.69 (br s, 2H).

[0393] **Step 2:** A mixture of 6-amino-1,3-benzothiazole-7-carbonitrile (500 mg, 2.85 mmol, 1.00 eq.), para-toluenesulfonic acid (590 mg, 3.42 mmol, 1.20 eq.), *tert*-butyl nitrite (353 mg, 3.42 mmol, 407 μL , 1.20 eq.), tetrabutylammonium bromide (1.84 g, 5.71 mmol, 2.00 eq.) and copper bromide (64 mg, 0.286 mmol, 0.10 eq.) in acetonitrile (15 mL) was degassed with nitrogen and stirred at 25 °C for 6 hours. The mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10-25%) to give 6-bromo-1,3-benzothiazole-7-carbonitrile (300 mg, 1.25 mmol, 44% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 240.9$; ^1H NMR (400 MHz, CDCl_3) $\delta = 9.11$ (s, 1H), 8.20 (d, $J = 8.8$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H).

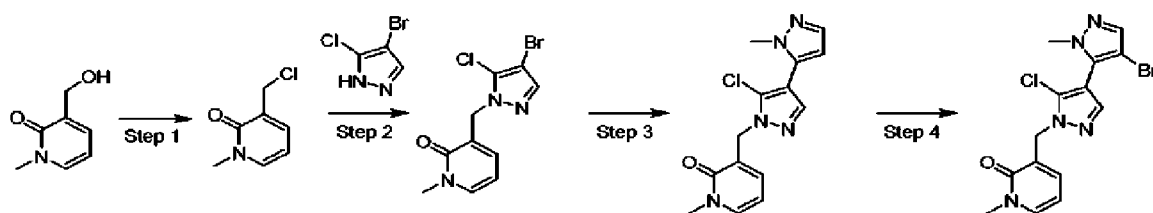
[0394] **Step 3:** A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (261 mg, 1.25 mmol, 1.00 eq.), 6-bromo-1,3-benzothiazole-7-carbonitrile (300 mg, 1.25 mmol, 1.00 eq.), *ditert*-butyl(cyclopentyl)phosphane, dichloropalladium iron (82 mg, 0.125 mmol, 0.10 eq.) and sodium bicarbonate (316 mg, 3.76 mmol, 3.00 eq.) in dioxane (10 mL) and water (2 mL) was degassed with nitrogen and then stirred at 80 °C for 3 hours under a nitrogen atmosphere. The mixture was then concentrated and the residue purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 5-25%) to give 6-(2-methylpyrazol-3-

yl)-1,3-benzothiazole-7-carbonitrile (280 mg, 0.89 mmol, 71% yield) as a yellow solid.

LCMS $[M+1]^+ = 241.0$; ^1H NMR (400 MHz, CDCl_3 -*d*) $\delta = 9.21$ (s, 1H), 8.43 (d, $J = 8.4$ Hz, 1H), 7.66 - 7.58 (m, 2H), 6.58 (d, $J = 2.0$ Hz, 1H), 3.91 (s, 3H).

[0395] **Step 4:** A mixture of 6-(2-methylpyrazol-3-yl)-1,3-benzothiazole-7-carbonitrile (140 mg, 0.58 mmol, 1.00 *eq.*), *N*-bromosuccinimide (207 mg, 1.17 mmol, 2.00 *eq.*) in acetonitrile (3 mL) was stirred at 40 °C for 2 hours under a nitrogen atmosphere. The mixture was then concentrated and the residue purified by column chromatography (SiO_2 , petroleum ether: ethyl 5-20%) to give 6-(4-bromo-2-methyl-pyrazol-3-yl)-1,3-benzothiazole-7-carbonitrile (300 mg, 0.47 mmol, 81% yield) as a white solid. LCMS $[M+1]^+ = 321.0$; ^1H NMR (400 MHz, CDCl_3 -*d*) $\delta = 9.25$ (s, 1H), 8.48 (d, $J = 8.4$ Hz, 1H), 7.65 (s, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 3.85 (s, 3H).

INTERMEDIATE EW



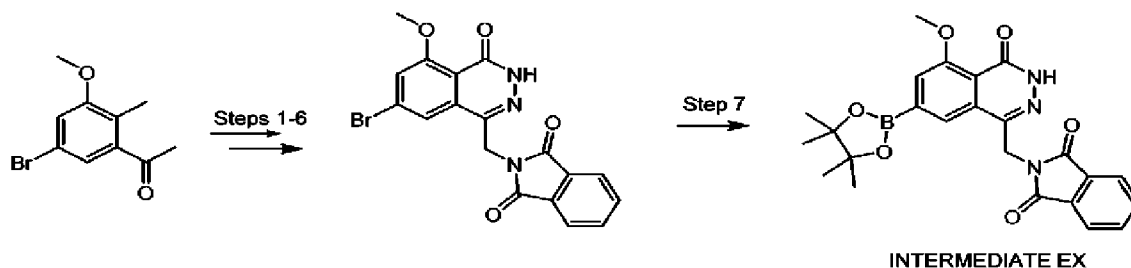
[0396] **Step 1:** To a solution of 3-(hydroxymethyl)-1-methylpyridin-2(1H)-one (650 mg, 4.67 mmol, 1.00 *eq.*) in dichloromethane (15 mL) was added thionyl chloride (667 mg, 5.61 mmol, 407 μL , 1.20 *eq.*) and the mixture was stirred at 25°C for 2 hrs. The mixture was concentrated in vacuum to give 3-(chloromethyl)-1-methylpyridin-2-one (650 mg, crude) as a white solid.

[0397] **Step 2:** To a solution of 3-(chloromethyl)-1-methylpyridin-2-one (650 mg, 4.12 mmol, 1.00 *eq.*), 4-bromo-5-chloro-1H-pyrazole (747 mg, 4.12 mmol, 1.00 *eq.*) in acetonitrile (20 mL) was added potassium carbonate (683 mg, 4.94 mmol, 1.20 *eq.*) and the mixture was stirred at 80 °C for 12 hours. The reaction was then quenched with water (100 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 5%) to give 3-[(4-bromo-5-chloro-pyrazol-1-yl)methyl]-1-methylpyridin-2-one (270 mg, 0.89 mmol, 51% yield) as a yellow solid. LCMS $[M+1]^+ = 304.0$.

[0398] **Step 3:** To a solution of 3-[(4-bromo-5-chloro-pyrazol-1-yl)methyl]-1-methylpyridin-2-one (270 mg, 0.89 mmol, 1.00 *eq.*), 4-bromo-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (512 mg, 1.78 mmol, 2.00 *eq.*) in dioxane (10 mL) and water (1 mL) was added Pd(dppf)Cl₂ (65 mg, 0.089 mmol, 0.10 *eq.*) and sodium bicarbonate (150 mg, 1.78 mmol, 69 μ L, 2.00 *eq.*). The mixture was stirred at 110 °C for 10 hours. The reaction mixture was then quenched by addition water (50 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Gemini-NX 80 mm $\times$ 40 mm $\times$ 3 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 5%-35%, 8 min) to give 3-[[5-chloro-4-(2-methylpyrazol-3-yl)pyrazol-1-yl]methyl]-1-methylpyridin-2-one (60.0 mg, 0.198 mmol, 22% yield) as a grey solid. LCMS [M+1]⁺ = 304.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.24 (s, 1H), 7.73 (d, *J* = 2.0, 6.8 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 5.2 Hz, 1H), 6.39 (d, *J* = 2.0 Hz, 1H), 6.25 (t, *J* = 6.8 Hz, 1H), 5.14 (s, 2H), 3.79 (s, 3H), 3.45 (s, 3H)

[0399] **Step 4:** To a solution of 3-((5'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)-1-methylpyridin-2(1*H*)-one (47.0 mg, 0.155 mmol, 1.00 *eq.*) in acetonitrile (1 mL) was added *N*-bromosuccinimide (26 mg, 0.147 mmol, 0.95 *eq.*). The mixture was stirred at 25 °C for 10 hours. The reaction mixture was then quenched by addition of water (5 mL) and extracted with ethyl acetate (5 mL $\times$ 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, dichloromethane: methanol 10%) to give 3-((4-bromo-5'-chloro-2-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-1'-yl)methyl)-1-methylpyridin-2(1*H*)-one (45 mg, 0.118 mmol, 76% yield) as a white solid. LCMS [M+1]⁺ = 383.9; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.89 (s, 1H), 7.71 (d, *J* = 6.8, 1.2 Hz, 1H), 7.67 (s, 1H), 6.93 - 6.96 (m, 1H), 6.23 (t, *J* = 6.8 Hz, 1H), 5.22 (s, 2H), 3.74 (s, 3H), 3.47 (s, 3H).

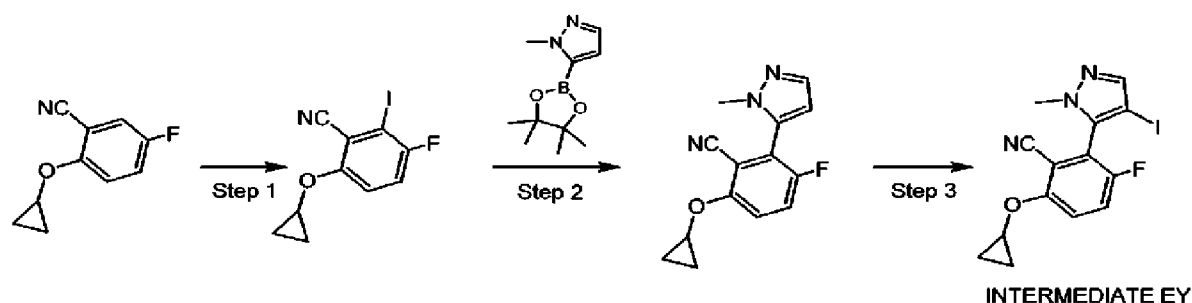
INTERMEDIATE EX



[0400] **Steps 1-6:** 2-((7-bromo-4-oxo-5-(methoxy)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione was prepared as a white solid (4.22 g, 10.2 mmol, 8% yield over 6 steps) starting from 1-(5-bromo-2-methyl-3-(methoxy)phenyl)ethan-1-one following the same procedure described for the first 6 steps of Intermediate DK. LCMS $[M+1]^+ = 414.0$.

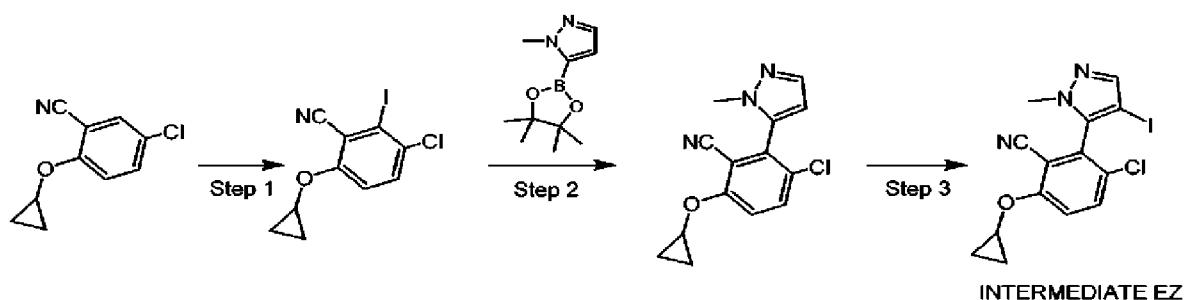
[0401] **Step 7:** A mixture of 2-((7-bromo-4-oxo-5-(methoxy)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione (4.22 g, 10.2 mmol, 1.0 eq.), bis(pinacolato)diboron (3.88 g, 15.3 mmol, 1.5 eq.), Pd(dppf)Cl₂ • CH₂Cl₂ (745 mg, 1.02 mmol, 0.1 eq.) and potassium acetate (3.00 g, 30.6 mmol, 3.0 eq.) in dioxane (60 mL) was degassed and purged with nitrogen 3 times, and stirred at 100 °C for 1 hour. The mixture was then concentrated, and the residue triturated with methanol, filtered and dried to give Intermediate EX as a grey solid (2.01 g, 43% yield). LCMS $[M+1]^+ = 380.1$ (boronic acid from loss of pinicol).

INTERMEDIATE EY



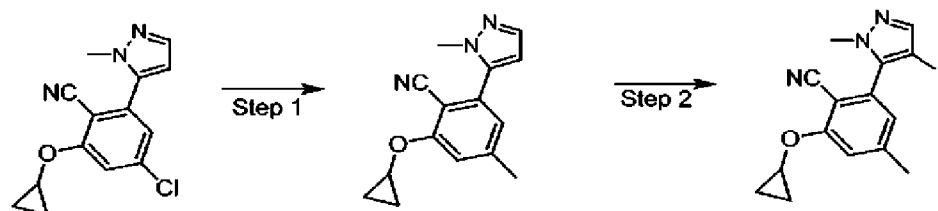
[0402] 6-cyclopropoxy-3-fluoro-2-(4-iodo-1-methyl-1H-pyrazol-5-yl)benzonitrile, intermediate EY, was prepared as a white solid (120 mg, 0.30 mmol, 20% over 3 steps) following the procedure described for the preparation of Intermediate DQ. LCMS $[M+1]^+ = 383.8$; ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (s, 1H), 7.51 - 7.40 (m, 2H), 3.93 - 3.87 (m, 1H), 3.83 (s, 3H), 1.00 - 0.89 (m, 4H).

INTERMEDIATE EZ



[0403] 6-cyclopropoxy-3-chloro-2-(4-iodo-1-methyl-1H-pyrazol-5-yl)benzonitrile, intermediate EZ, was prepared as a yellow solid (160 mg, 0.40 mmol, 22% over 3 steps) following the procedure described for the preparation of Intermediate DQ. LCMS $[M+1]^+ = 399.9$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.70$ (d, $J = 9.2$ Hz, 1H), 7.64 (s, 1H), 7.47 (d, $J = 9.2$ Hz, 1H), 3.92 (td, $J = 2.8, 5.6$ Hz, 1H), 3.78 (s, 3H), 0.99 - 0.90 (m, 4H).

INTERMEDIATE FA

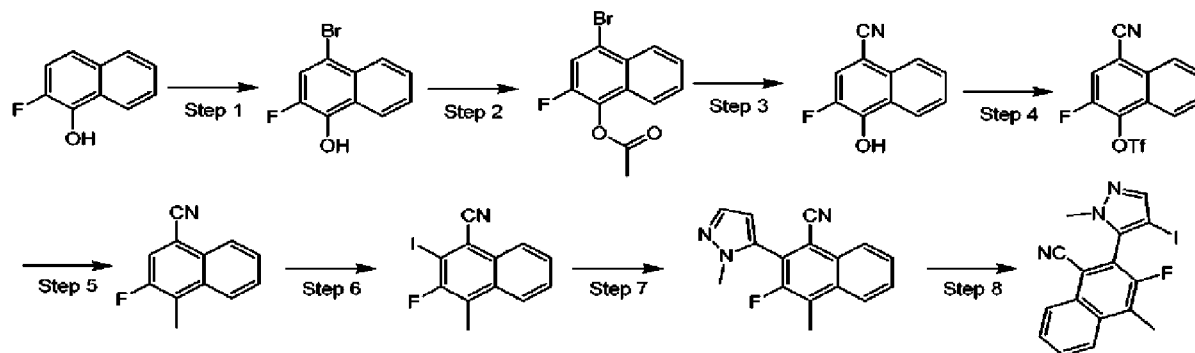


[0404] **Step 1:** To a solution of 4-chloro-2-(cyclopropoxy)-6-(1-methyl-1H-pyrazol-5-yl)benzonitrile (177 mg, 0.65 mmol, 1.00 *eq.*) in dioxane (10 mL) was added potassium carbonate (268 mg, 1.94 mmol, 3.00 *eq.*), *ditert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (42 mg, 0.064 mmol, 0.10 *eq.*) and methylboronic acid (194 mg, 3.23 mmol, 5.00 *eq.*). The mixture was stirred at 100 °C for 2 hours then diluted with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 25%) to give 2-(cyclopropoxy)-4-methyl-6-(2-methylpyrazol-3-yl)benzonitrile (111 mg, 0.44 mmol, 68% yield) as a white solid. LCMS $[M+1]^+ = 254.1$; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.98$ (d, $J = 2.0$ Hz, 1H), 7.65 (d, $J = 0.8$ Hz, 1H), 7.27 (s, 1H), 6.85 (d, $J = 2.0$ Hz, 1H), 4.35 - 4.29 (m, 1H), 4.27 (s, 3H), 2.91 (s, 3H), 1.36 - 1.31 (m, 4H).

[0405] **Step 2:** To a solution of 2-(cyclopropoxy)-4-methyl-6-(2-methylpyrazol-3-yl)benzonitrile (100 mg, 0.40 mmol, 1.00 *eq.*) in acetic acid (2 mL) was added *N*-iodosuccinimide (178 mg, 0.79 mmol, 2.00 *eq.*). The mixture was stirred at 25 °C for 1 hour then diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 25%) to give 2-(cyclopropoxy)-6-(4-iodo-2-methylpyrazol-3-yl)-4-methylbenzonitrile (94 mg, 0.25 mmol, 63% yield) as a yellow solid. LCMS $[M+1]^+ = 380.0$; ^1H NMR (400 MHz,

CDCl_3) δ = 7.66 - 7.55 (m, 1H), 7.27 (s, 1H), 6.80 (s, 1H), 3.89 (tt, J = 3.2, 6.0 Hz, 1H), 3.85 - 3.79 (m, 3H), 2.50 (s, 3H), 1.04 - 0.80 (m, 4H).

INTERMEDIATE FB



[0406] **Step 1:** To a solution of 2-fluoronaphthalen-1-ol (0.50 g, 3.08 mmol, 1.00 *eq.*) in dichloromethane (8 mL) was added NBS (521 mg, 2.93 mmol, 0.95 *eq.*) and the mixture was stirred at -50 °C for 0.25 hr. Water (10 mL) was then added and the separated organic phase was dried, concentrated and the residue purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 1%) to give 4-bromo-2-fluoro-naphthalen-1-ol (500 mg, 2.07 mmol, 67% yield) as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.27 - 8.21 (m, 1H), 8.19 - 8.11 (m, 1H), 7.63 (d, J = 10.2 Hz, 1H), 7.61 - 7.54 (m, 2H), 5.68 (br d, J = 4.0 Hz, 1H).

[0407] **Step 2:** To a solution of 4-bromo-2-fluoro-naphthalen-1-ol (2.30 g, 9.54 mmol, 1.00 *eq.*), DIEA (21.0 mmol, 3.66 mL, 2.20 *eq.*) and DMAP (58 mg, 0.48 mmol, 0.05 *eq.*) in dichloromethane (40 mL) at 0 °C was added acetyl chloride (19.1 mmol, 1.36 mL, 2.00 *eq.*) in a dropwise fashion. The mixture was stirred at 28 °C for 1 hr before the mixture was concentrated and the formed residue purified by column chromatography (SiO_2 , pether/ethyl acetate 1%) to give (4-bromo-2-fluoro-1-naphthyl) acetate (2.50 g, 8.83 mmol, 93% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.26 - 8.18 (m, 1H), 7.94 - 7.86 (m, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.66 - 7.56 (m, 2H), 2.51 (s, 3H).

[0408] **Step 3:** A mixture of (4-bromo-2-fluoro-1-naphthyl) acetate (2.50 g, 8.83 mmol, 1.00 *eq.*), $\text{Pd}_2(\text{dba})_3$ (809 mg, 0.88 mmol, 0.10 *eq.*), $\text{Zn}(\text{CN})_2$ (9.71 mmol, 0.62 mL, 1.10 *eq.*), Zn (29 mg, 0.442 mmol, 0.05 *eq.*) and DPPF (979 mg, 1.77 mmol, 0.20 *eq.*) in DMA (40 mL) was degassed with nitrogen 3 times then stirred at 120 °C for 3 hr. The reaction mixture was then diluted with ethyl acetate (100 mL), filtered and the filtrate was washed with brine (50 mL $\times$ 3), dried, concentrated and the residue was purified by column chromatography (SiO_2 ,

petroleum ether/ethyl acetate 2-10%) to give 3-fluoro-4-hydroxy-naphthalene-1-carbonitrile (980 mg, 5.24 mmol, 59% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.36 - 8.27 (m, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 9.6 Hz, 1H), 7.72 - 7.62 (m, 2H).

[0409] **Step 4:** To a solution of 3-fluoro-4-hydroxy-naphthalene-1-carbonitrile (880 mg, 4.70 mmol, 1.00 *eq.*) in dichloromethane (20 mL) was added triethylamine (9.40 mmol, 1.31 mL, 2.00 *eq.*) and Tf₂O (8.46 mmol, 1.40 mL, 1.80 *eq.*) at 0 °C. The mixture was then stirred at 28 °C for 0.5 hr. The reaction mixture was then concentrated, and the residue purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 2%) to give (4-cyano-2-fluoro-1-naphthyl) trifluoromethanesulfonate (1.15 g, 3.60 mmol, 77% yield) as a yellow solid.

[0410] **Step 5:** A mixture of (4-cyano-2-fluoro-1-naphthyl) trifluoromethanesulfonate (0.38 g, 1.19 mmol, 1.00 *eq.*), Pd(PPh₃)₄ (138 mg, 0.12 mmol, 0.10 *eq.*), AlMe₃ (2 M in PhMe, 1.79 mL, 3.00 *eq.*) in toluene (3.5 mL) was degassed with nitrogen 3 times and stirred at 120 °C for 2 hr. After such time the reaction was quenched by the addition of water (5 mL) then diluted with ethyl acetate (40 mL) and filtered. The filtrate was washed with water (20 mL × 3), dried, concentrated and the residue purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate 5%) to give compound 3-fluoro-4-methyl-naphthalene-1-carbonitrile (90 mg, 0.49 mmol, 41% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.29 - 8.22 (m, 1H), 8.11 - 8.03 (m, 1H), 7.75 - 7.63 (m, 3H), 2.66 (d, *J* = 2.4 Hz, 3H).

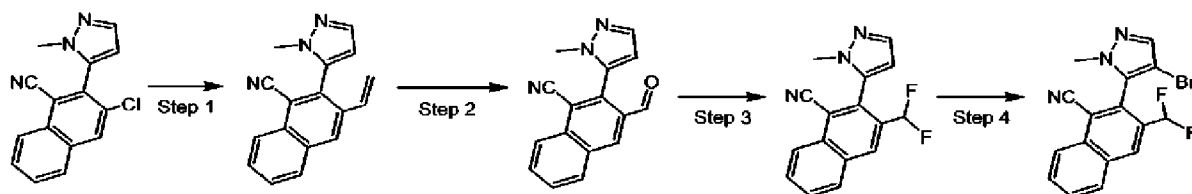
[0411] **Step 6:** To a solution of *N*-isopropylpropan-2-amine (0.86 mmol, 0.12 mL, 2.00 *eq.*) in THF (2 mL) was added *n*-BuLi (2.5 M in THF, 0.31 mL, 1.80 *eq.*) in a dropwise fashion at -70 °C. The mixture was then stirred at -70 °C for 0.5 hr, then 3-fluoro-4-methyl-naphthalene-1-carbonitrile (80 mg, 0.43 mmol, 1 *eq.*) was added and stirred for a further 0.5 hr before iodine (0.87 mmol, 0.17 mL, 2.00 *eq.*) was added. After completion of the addition the mixture was stirred at 30 °C for 1 hr. The reaction mixture was then quenched by the addition of water (2 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic phases were dried and concentrated to give 3-fluoro-2-iodo-4-methyl-naphthalene-1-carbonitrile (110 mg, 0.35 mmol) as a brown solid.

[0412] **Step 7:** A mixture of 3-fluoro-2-iodo-4-methyl-naphthalene-1-carbonitrile (110 mg, 0.35 mmol, 1.00 *eq.*), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (96 mg, 0.46 mmol, 1.30 *eq.*), [2-(2-aminophenyl)phenyl]palladium(1+)-bis(1-adamantyl)-butylphosphane-methanesulfonate (26 mg, 0.035 mmol, 0.10 *eq.*), K₃PO₄ (1.50 M, 0.71 mL, 3.00 *eq.*) in *n*-butyl alcohol (2.8 mL) was degassed with nitrogen 3 times then stirred at 60 °C for 6

hr. The reaction mixture was then filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate 20%) to give 3-fluoro-4-methyl-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (50 mg, 0.19 mmol, 53% yield) as a brown solid. LCMS [M+1]⁺ 266.1.

[0413] **Step 8:** To a solution of 3-fluoro-4-methyl-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (50 mg, 0.19 mmol, 1.00 *eq.*) in acetic acid (2 mL) was added NIS (127 mg, 0.57 mmol, 3.00 *eq.*). The mixture was stirred at 30 °C for 12 hrs. The pH was then adjusted to pH 7 with saturated sodium bicarbonate aqueous solution and then extracted with ethyl acetate (10 mL × 3) and the combined organic phases were dried and concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate 20%) to give compound 3-fluoro-2-(4-iodo-2-methyl-pyrazol-3-yl)-4-methyl-naphthalene-1-carbonitrile (30 mg, 0.076 mmol, 41% yield) as a brown solid. LCMS [M+1]⁺ 392.0.

INTERMEDIATE FC



[0414] **Step 1:** To a solution of 3-chloro-2-(1-methyl-1*H*-pyrazol-5-yl)-1-naphthonitrile (200 mg, 0.747 mmol, 1.00 *eq.*), potassium trifluoro(vinyl)borate (120 mg, 0.896 mmol, 1.20 *eq.*), cesium carbonate (730 mg, 2.24 mmol, 3.00 *eq.*) and dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine (34.9 mg, 0.074 mmol, 0.10 *eq.*) in THF (2 mL) and water (0.2 mL) was added palladium(II) chloride (13.3 mg, 0.074 mmol, 0.10 *eq.*) under a nitrogen atmosphere. The resulting mixture was stirred at 90 °C for 16 hours. The mixture was then diluted with water (3 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 5-20%) to give 2-(1-methyl-1*H*-pyrazol-5-yl)-3-vinyl-1-naphthonitrile (130 mg, 0.049 mmol, 66% yield) as a light yellow solid. LCMS [M+1]⁺ = 260.2.

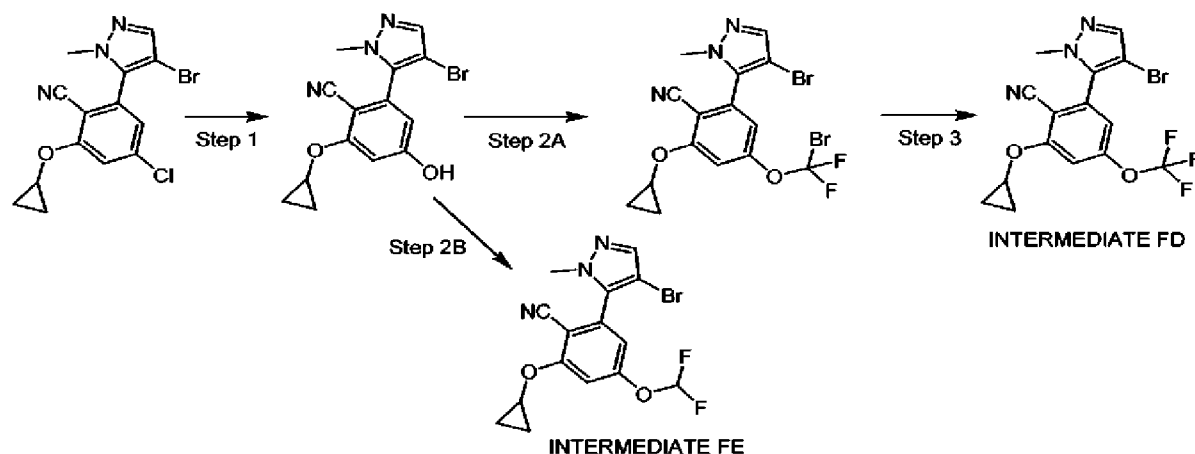
[0415] **Step 2:** 2-(1-methyl-1*H*-pyrazol-5-yl)-3-vinyl-1-naphthonitrile (130 mg, 491 μmol, 1.00 *eq.*) were dissolved in dichloromethane (20 mL) and cooled to -70 °C. Ozone was

bubbled into the reaction solution with stirring for 15 min. Dimethylsulfane (8.46 g, 136 mmol, 10 mL, 277 *eq*) was then added and the mixture stirred at -70 °C for 15 min. After such time the mixture was concentrated and then purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 5-20%) to give 3-formyl-2-(1-methyl-1*H*-pyrazol-5-yl)-1-naphthonitrile (60 mg, 222 μmol, 45.3% yield) as a white solid. LCMS [M+1]⁺ = 262.2.

[0416] **Step 3:** A solution of 3-formyl-2-(1-methyl-1*H*-pyrazol-5-yl)-1-naphthonitrile (20 mg, 74.2 μmol, 1.00 *eq*) and (bis-(2-methoxyethyl)amino)sulfur trifluoride (41 mg, 185 μmol, 41 μL, 2.50 *eq*) in dichloromethane (1.0 mL) was stirred at 25 °C for 6 hours. The reaction was then quenched with saturated sodium bicarbonate aqueous (2 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed by brine (3 mL × 3), dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by Prep-TLC (Petroleum ether/Ethyl acetate 20%) to give 3-(difluoromethyl)-2-(2-methylpyrazol-3-yl)naphthalene-1-carbonitrile (11.0 mg, 38.4 μmol, 52% yield) as a white solid. LCMS [M+1]⁺ = 284.2.

[0417] **Step 4:** To a solution of 3-(difluoromethyl)-2-(1-methyl-1*H*-pyrazol-5-yl)-1-naphthonitrile (11 mg, 38 μmol, 1.00 *eq*) in dichloromethane (1.0 mL) was added 1-bromopyrrolidine-2,5-dione (10 mg, 58 μmol, 1.50 *eq*). The mixture was stirred at 25 °C for 10 hours. The reaction mixture was the concentrated and purified by Prep-TLC (SiO₂, Petroleum ether/Ethyl acetate 20%) to give 2-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-3-(difluoromethyl)-1-naphthonitrile (12 mg, 33 μmol, 86% yield) as a colorless oil. LCMS [M+1]⁺ = 362.1.

INTERMEDIATES FD and FE



[0418] **Step 1:** A mixture of sodium hydride (51 mg, 1.28 mmol, 60% purity, 1.20 *eq.*) and 2-methylsulfonylethanol (158 mg, 1.28 mmol, 1.20 *eq.*) in DMF (3 mL) at 0 °C under nitrogen was stirred at 0 °C for 30 minutes. Then, a solution of 2-(4-bromo-2-methyl-pyrazol-3-yl)-4-chloro-6-(cyclopropoxy)benzonitrile (375 mg, 1.06 mmol, 1 *eq.*) in DMF (2 mL) was added dropwise and the reaction mixture was stirred at 25 °C for 2 hours. The mixture was then quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated and purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 10-30%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-4-hydroxy-benzonitrile (120 mg, 33% yield) as colorless oil. LCMS [M+1]⁺=334.0; ¹H NMR (400 MHz, CDCl₃) δ = 9.77 - 9.37 (m, 1H), 7.54 (s, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 3.85 - 3.82 (m, 1H), 3.80 (s, 3H), 0.94 - 0.84 (m, 5H).

[0419] **Step 2A:** To a mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-4-hydroxy-benzonitrile (20 mg, 59 μmol, 1.00 *eq.*) in DMF (0.5 mL) was added sodium hydride (4.8 mg, 119 μmol, 60% purity, 2.00 *eq.*) at 0 °C under nitrogen and the mixture was stirred at 0 °C for 30 minutes. Then dibromo(difluoro)methane (38 mg, 180 μmol, 17 uL, 3.00 *eq.*) was added to the mixture at 0 °C and the mixture was stirred at 25 °C for 1 hour. Water (3.00 mL) was then added and the mixture extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated under vacuum and the residue was purified by prep-TLC (SiO₂, petroleum ether: ether acetate 20%) to give 4-[bromo(difluoro)methoxy]-2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)benzonitrile (10.0 mg, 36% yield) as a white solid. LCMS [M+1]⁺=463.9

[0420] **Step 2B:** To a mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-4-hydroxy-benzonitrile (100 mg, 299 μmol, 1.00 *eq.*) and sodium 2-chloro-2,2-difluoro-acetate (114 mg, 748 μmol, 2.50 *eq.*) in DMF (1.0 mL) and water (0.1 mL) was added cesium carbonate (146 mg, 449 μmol, 1.50 *eq.*). The mixture was stirred at 100 °C for 3 hours. The reaction mixture was then quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried with anhydrous sodium sulfate, filtered, concentrated in vacuum and the residue purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 0-30%) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-4-(difluoromethoxy)benzonitrile (70 mg, 61% yield) as colorless oil. LCMS [M+1]⁺=386.0; ¹H NMR (400 MHz, CDCl₃) δ = 7.57 (s, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.87 - 6.43 (m, 2H), 3.95 - 3.87 (m, 1H), 3.82 (s, 3H), 0.99 - 0.90 (m, 4H)

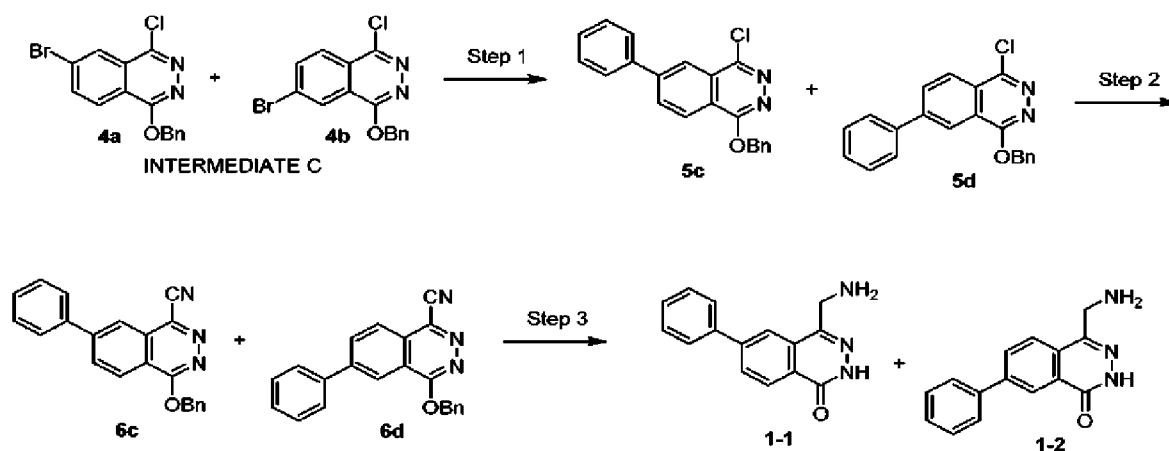
[0421] **Step 3:** A mixture of 4-[bromo(difluoro)methoxy]-2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)benzonitrile (100 mg, 216 μmol , 1.00 *eq.*) and silver tetrafluoroborate (273 mg, 1.40 mmol, 6.50 *eq.*) in DCE (2. mL) was stirred at 65 °C for 3 hours. Then, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (15 mL), dried with anhydrous sodium sulfate, filtered, concentrated in vacuum and the residue purified by reversed phase flash (0.1% FA condition) to give 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-(cyclopropoxy)-4-(trifluoromethoxy)benzonitrile (55 mg, 63% yield) as a yellow solid. LCMS $[M+1]^+ = 402.1$.

[0422] In one aspect of the invention, provided herein are Intermediates that may be used in the preparation of compounds of Formula (I), Formula (I-A), Formula (I-B), Formula (I-C) and Formula (I-D). In one embodiment, the intermediates include Intermediates A-1 through FE.

[0423] The following Examples are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

GENERAL REACTION METHODS FOR THE PREPARATION OF EXAMPLES 1-1 to 1-8

EXAMPLES 1-1 and 1-2



[0424] **Step 1:** A mixture of Intermediate C, a 1:1 mixture of 4c and 4d (587 mg, 1.68 mmol, 1.00 *eq.*), phenylboronic acid pinacol ester, Pd(dppf)Cl₂ (168 μmol , 0.10 *eq.*) and sodium carbonate (3.36 mmol, 2.00 *eq.*) in DMF (10 mL) was purged with nitrogen 3 times and stirred at 100 °C for 2 hours. After such time the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were

washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 5: 1) to give a 1:1 mixture of 4-(benzyloxy)-1-chloro-7-phenylphthalazine **5c** and **5d** 4-benzyloxy-1-chloro-6-phenyl-phthalazine (355 mg, 818 μ mol, 48% yield) as a yellow solid.

[0425] **Step 2:** To a 1:1 mixture of 4-(benzyloxy)-1-chloro-6-phenylphthalazine **5c** and 4-(benzyloxy)-1-chloro-7-phenylphthalazine **5d** (350 mg, 806 μ mol, 1.00 eq.) in DMF (10 mL) was added zinc cyanide (1.21 mmol, 1.50 eq.), 1,1'-bis(diphenylphosphino)ferrocene (80.6 μ mol, 0.10 eq.), Pd₂(dba)₃ (40.3 μ mol, 0.05 eq.) and zinc powder (80.6 μ mol, 0.10 eq.). The mixture was purged with nitrogen 3 times and stirred at 100 °C for 3 hours. After such time the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a residue. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10: 1 to 3: 1) to give a 1:1 mixture of 4-(benzyloxy)-7-phenylphthalazine-1-carbonitrile **6c** and 4-benzyloxy-6-phenyl-phthalazine-1-carbonitrile **6d** (158 mg, 468 μ mol, 58% yield) as a yellow solid.

[0426] **Step 3:** To a 1:1 mixture of 4-(benzyloxy)-7-phenylphthalazine-1-carbonitrile **6c** and 4-(benzyloxy)-6,6-phenylphthalazine-1-carbonitrile **6d** (100 mg, 296 μ mol, 1.00 eq.) was added hydrochloric acid (6.00 M, 10.1 eq.) and methyl alcohol (3.00 mL) followed by palladium on activated carbon (29.6 μ mol, 10% by mass) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was then stirred under a hydrogen atmosphere (50 psi) at 40 °C for 2 hours. After such time the reaction mixture was filtered, concentrated under reduced pressure and the residue purified by prep-HPLC (Phenomenex Luna C18 150 $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (0.1%TFA)-ACN]; B%: 2%-25%, 10 min) followed by separation of the regioisomers by SFC (column: DAICEL CHIRALPAK AD (250 mm $\times$ 30 mm, 10 μ m); mobile phase: [0.1% NH₄H₂O MeOH]; B%: 60%-60%, 40 min] to give the desired compounds 4-(aminomethyl)-6-phenyl-phthalazin-1-ol, Example 1-1 (13.7 mg, 53.6 μ mol, 26% yield) LCMS [M+1] = 252.2; ¹H NMR (400 MHz, MeOD) δ = 8.37 (d, J = 8.0 Hz, 1H), 8.09 - 8.02 (m, 2H), 7.76 (d, J = 7.2 Hz, 2H), 7.54 - 7.48 (m, 2H), 7.47 - 7.41 (m, 1H), 4.22 (s, 2H). LCMS [M+1]: 252.2 and 4-(aminomethyl)-7-phenyl-phthalazin-1-ol, Example 1-2 (23.6 mg, 91.8 μ mol, 46% yield) LCMS [M+1]: 252.3; ¹H NMR (400 MHz, MeOD) δ = 8.64 (d, J = 2.0 Hz, 1H), 8.28 (dd, J

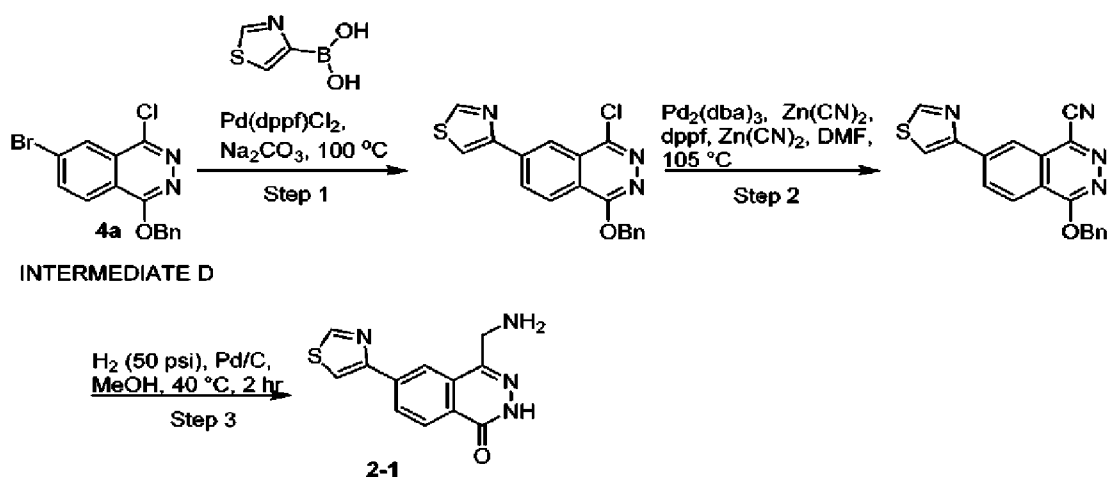
= 2.0, 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.83 - 7.74 (d, J = 7.2 Hz, 2H), 7.58 - 7.51 (m, 2H), 7.50 - 7.44 (m, 1H), 4.61 (s, 2H).

[0427] Following the teachings of the General Reaction Schemes, the synthesis procedure for Examples 1-1 & 1-2 and using the Intermediates disclosed herein, the Examples 1-3 to 1-8 were prepared as shown in Table 1:

Table 1

Example	Structure	Compound Name and Characterization
1-3		4-(aminomethyl)-6-(pyridin-2-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.2; ¹ H NMR (400 MHz, MeOD) δ = 8.76 - 8.72 (m, 1H), 8.55 (s, 1H), 8.50 - 8.43 (m, 2H), 8.14 - 8.09 (m, 1H), 8.00 (dt, J = 2.0, 7.6 Hz, 1H), 7.49 (ddd, J = 0.8, 5.2, 7.6 Hz, 1H), 4.29 (br s, 2H)
1-4		4-(aminomethyl)-7-(pyridin-2-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.2; ¹ H NMR (400 MHz, MeOD) δ = 8.96 (d, J = 1.6 Hz, 1H), 8.74 - 8.70 (m, 1H), 8.60 (dd, J = 2.0, 8.4 Hz, 1H), 8.12 - 8.05 (m, 2H), 8.02 - 7.95 (m, 1H), 7.46 (ddd, J = 1.2, 4.8, 7.6 Hz, 1H), 4.28 (s, 2H).
1-5		4-(aminomethyl)-6-(pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.2; ¹ H NMR (400 MHz, MeOD) δ = 8.91 (dd, J = 0.8, 2.4 Hz, 1H), 8.54 (dd, J = 1.6, 4.8 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.24 - 8.18 (m, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.09 (dd, J = 1.6, 8.4 Hz, 1H), 7.52 (ddd, J = 0.8, 4.8, 8.0 Hz, 1H), 4.24 (s, 2H).
1-6		4-(aminomethyl)-7-(pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.2; ¹ H NMR (400 MHz, MeOD) δ = 8.95 (d, J = 1.6 Hz, 1H), 8.66 - 8.60 (m, 2H), 8.32 - 8.22 (m, 2H), 8.11 (d, J = 8.4 Hz, 1H), 7.60 (ddd, J = 0.8, 4.8, 8.0 Hz, 1H), 4.23 (s, 2H).
1-7		4-(aminomethyl)-6-(1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 256.2; ¹ H NMR (400 MHz, MeOD) δ = 8.38 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H), 8.16 - 8.10 (m, 2H), 8.05 (s, 1H), 4.64 (s, 2H), 3.99 (s, 3H)
1-8		4-(aminomethyl)-7-(1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 256.2; ¹ H NMR (400 MHz, MeOD) δ = 8.50 (d, J = 2.0 Hz, 1H), 8.23 (s, 1H), 8.18 (dd, J = 2.0, 8.4 Hz, 1H), 8.02 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 4.57 (s, 2H), 3.98 (s, 3H).

EXAMPLE 2-1



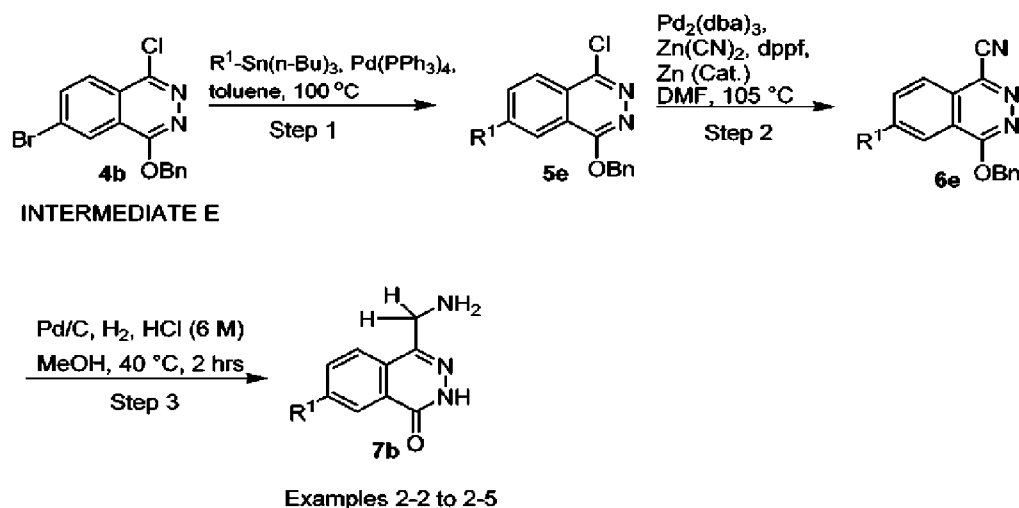
[0428] **Step 1:** A mixture of Intermediate D (150 mg, 429 μ mol, 1.00 eq.), thiazol-4-ylboronic acid (66 mg, 515 μ mol, 1.20 eq.), sodium carbonate (91 mg, 858 μ mol, 2.00 eq.) and Pd(dppf)Cl₂ (31 mg, 42.9 μ mol, 0.10 eq.) in DMF (1.00 mL) was purged with nitrogen 3 times and stirred at 100 °C for 12 hours under nitrogen. After such time the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to a residue. The residue was then purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5: 1 to 1: 1) to give 4-(1-(benzyloxy)-4-chlorophthalazin-6-yl)thiazole (76 mg, 214 μ mol, 50% yield).

[0429] **Step 2:** A mixture of 4-(1-(benzyloxy)-4-chlorophthalazin-6-yl)thiazole (76 mg, 214 μ mol, 1.00 eq.), zinc cyanide (38 mg, 321 μ mol, 20 μ L, 1.50 eq.), DPPF (12 mg, 21 μ mol, 0.10 eq.), Pd₂(dba)₃ (10 mg, 10 μ mol, 0.05 eq.) and zinc powder (1 mg, 21 μ mol, 0.10 eq.) in DMF (1.00 mL) was degassed and purged with nitrogen 3 times. The mixture was then stirred at 105 °C for 2 hours under a nitrogen atmosphere. After such time the reaction mixture was diluted with water (20 mL), extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic layers washed with brine (30 mL), dried (Na₂SO₄ anhydrous), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate= 5: 1 to 1: 1) to give 4-(benzyloxy)-7-(thiazol-4-yl)phthalazine-1-carbonitrile (51 mg, 148 μ mol, 69% yield).

[0430] **Step 3:** To a solution of 4-(benzyloxy)-7-(thiazol-4-yl)phthalazine-1-carbonitrile (103 mg, 299 μ mol, 1.00 eq), HCl (6.0 M, 1.00 eq.) in MeOH (10 mL) was added palladium

on activated carbon (296 μmol , 10.0% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was then stirred vigorously in a hydrogen atmosphere (50.0 psi) at 40 °C for 2 hours. After such time the reaction mixture was filtered, concentrated under reduced pressure and purified by prep-HPLC (Waters Xbridge 150 $\times$ 25 mm $\times$ 5 μm ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 12%-42%, 10 min) to furnish 4-(aminomethyl)-6-(thiazol-4-yl)phthalazin-1(2H)-one, Example 2-1 (3 mg, 12 μmol , 4% yield, 97% purity) as a white solid. LCMS [M+1]: 259.2; ^1H NMR (400 MHz, MeOD) δ = 9.17 (d, J = 2.0 Hz, 1H), 8.56 (s, 1H), 8.47 - 8.43 (m, 2H), 8.33 (d, J = 2.0 Hz, 1H), 4.29 (s, 2H).

GENERAL REACTION METHOD 2 FOR THE PREPARATION OF EXAMPLES 2-2 to 2-5



wherein R^1 = Aryl or Heteroaryl

[0431] **Step 1:** A mixture of Intermediate E (429 μmol , 1.00 eq.), the appropriate aryl/heteroaryl-tributyltin reagent (644 μmol , 1.50 eq) and $\text{Pd}(\text{PPh}_3)_4$ (43 μmol , 0.10 eq.) in toluene (2 mL) was purged with nitrogen 3 times and stirred at 100 °C for 12 hours. After such time the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a residue. The residue was then purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 5: 1 to 1: 1) to give appropriate R^1 -coupled product 5e.

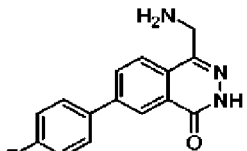
[0432] **Step 2:** A mixture of the R¹-coupled product **5e** (214 μ mol, 1.00 eq.), zinc cyanide (321 μ mol, 20 μ L, 1.50 eq.), DPPF (21 μ mol, 0.10 eq.), Pd₂(dba)₃ (10 μ mol, 0.05 eq.) and zinc powder (21 μ mol, 0.10 eq.) in DMF (1.00 mL) was purged with nitrogen 3 times. The mixture was then stirred at 105 °C for 2 hours. After such time the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a residue. The concentrated residue was then purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5: 1 to 1: 1) to give the appropriate R¹-cyanide **6e** which were used in the next step without further purification.

[0433] **Step 3:** To a solution of the appropriate R¹-cyanide **6e** (287 μ mol, 1.00 eq), HCl (6.0 M, 1.00 eq.) in MeOH (10 mL) was added palladium on activated carbon (296 μ mol, 10% Pd) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was then vigorously stirred under a hydrogen atmosphere (50 psi) at 40 °C for 2 hours before being filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Waters Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 12% - 42%, 10 min) to return the desired compounds shown in Table 2.

[0434] Following the teachings of the General Reaction Schemes, the general reaction method 2 and the Intermediates disclosed herein, the Examples 2-2 to 2-5 are prepared as shown in Table 2.

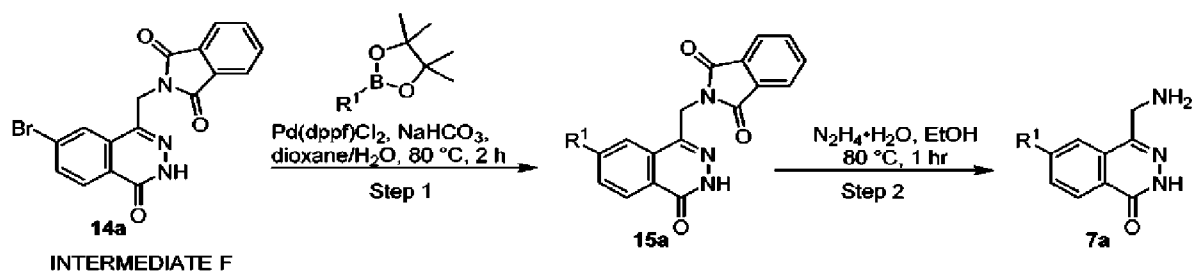
Table 2

Example	Structure	Compound Name and Characterization
2-2		4-(aminomethyl)-7-(pyridin-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.2; ¹ H NMR (400 MHz, MeOD) δ = 8.73 (d, J = 2.0 Hz, 1H), 8.71 - 8.68 (m, 2H), 8.34 (dd, J = 2.0, 8.4 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.89 - 7.86 (m, 2H), 4.21 (s, 2H).
2-3		4-(aminomethyl)-7-(2-fluorophenyl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.2; ¹ H NMR (400 MHz, MeOD) δ = 8.55 (s, 1H), 8.19 - 8.14 (m, 1H), 8.11 - 8.06 (m, 1H), 7.63 (dt, J = 1.6, 8.0 Hz, 1H), 7.52 - 7.45 (m, 1H), 7.35 (dt, J = 1.2, 7.6 Hz, 1H), 7.28 (ddd, J = 1.2, 8.4, 11.2 Hz, 1H), 4.25 (s, 2H).
2-4		4-(aminomethyl)-7-(3-fluorophenyl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.2; ¹ H NMR (400 MHz, MeOD) δ = 8.62 (d, J = 2.0 Hz, 1H), 8.25 (dd, J = 2.0, 8.6 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.60 - 7.53 (m, 2H), 7.26 - 7.18 (m, 1H), 4.22 (s, 2H).

2-5		4-(aminomethyl)-7-(4-fluorophenyl)phthalazin-1(2H)-one LCMS $[M+1]^+ = 270.2$; ^1H NMR (400MHz, MeOD) $\delta = 8.58$ (d, $J = 2.0$ Hz, 1H), 8.22 (dd, $J = 2.0, 8.6$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.86 - 7.78 (m, 2H), 7.33 - 7.25 (m, 2H), 4.24 (s, 2H).

**GENERAL COUPLING METHODS (CM) AND PURIFICATION METHODS (PM) FOR
THE PREPARATION OF EXAMPLES 3-1 to 3-61**

CM 3A

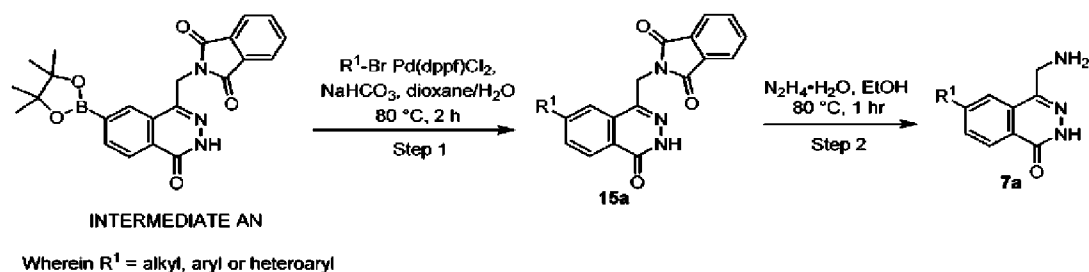


R^1 = aryl, heteroaryl, alkyl

[0435] **Step 1:** A mixture of the appropriate aryl/heteroaryl/alkyl-boronic ester (390 μmol , 1.5 *eq.*), intermediate F (260 μmol , 1.00 *eq.*), Pd(dppf)Cl_2 (26 μmol , 0.10 *eq.*), sodium bicarbonate (43 mg, 521 μmol , 20.3 μL , 2.00 *eq.*) in dioxane (1.00 mL) and water (0.20 mL) was purged with nitrogen 3 times. The mixture was then stirred at 80 °C for 2 hours. After such time the mixture was filtered, washed with a dichloromethane: methyl alcohol 10:1 mixture and the filtrate concentrated under reduced pressure. The concentrated residue was then triturated with methyl alcohol (3.00 mL) to give the corresponding Suzuki coupling product **15a** as a black solid.

[0436] **Step 2:** To a solution of corresponding Suzuki coupling product **15a** in ethyl alcohol (1.00 mL) was added hydrazine hydrate (242 μmol , 14 μL). The mixture was stirred at 80 °C for 1 hour, cooled and concentrated under reduced pressure. The concentrated residue was then purified by prep-HPLC according to one of the purification methods 3-1, 3-2, 3-3 or 3-4 described herein to furnish **7a**.

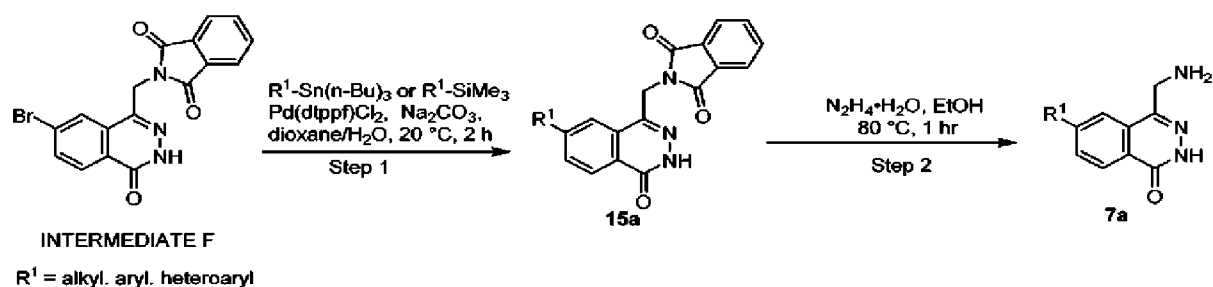
CM 3B:



[0437] **Step 1:** Intermediate AN, the appropriate alkyl/aryl/heteroaryl bromide (464 μmol), sodium bicarbonate (464 μmol , 18.0 μL , 2.00 *eq.*) and Pd(dppf)Cl₂ (17 mg, 23 μmol , 0.10 *eq.*) in dioxane (2 mL) and water (0.40 mL) was purged with nitrogen 3 times. The mixture was then stirred at 80 °C for 1 hour. After such time the reaction mixture was diluted with water (2 mL), filtered under reduced pressure and the filter cake triturated with ethyl alcohol (3 mL) to give the corresponding R¹-Suzuki coupling product **15a** as a black solid which was directly in the next step without further purification.

[0438] **Step 2:** To a solution of corresponding R¹-Suzuki coupling product **15a** in ethyl alcohol (1.00 mL) was added hydrazine hydrate (242 μmol , 14 μL). The mixture was stirred at 80 °C for 1 hour. After such time the mixture was concentrated under reduced pressure and the residue purified by prep-HPLC according to one of the purification methods 3-1 to 3-4.

CM 3C



[0439] **Step 1:** A mixture of Intermediate F (312 μmol , 1.00 *eq.*), the appropriate alkyl/aryl/heteroaryl tributyltin or alkyl/aryl/heteroaryl trimethyl silicon reagent (625 μmol , 2.00 *eq.*), Pd(PPh₃)₄ (72 mg, 62 μmol , 0.20 *eq.*) in dioxane (3.00 mL) was purged with nitrogen 3 times. The mixture was then stirred at 100 °C for 1 hour. After such time the reaction mixture was diluted with a potassium fluoride solution (3.0 mL) to form a suspension. The suspension was filtered, and the filtrate extracted with ethyl acetate (8 mL $\times$

3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 10:1) to give the corresponding C-C bond formation compound **15a** as a black solid.

[0440] **Step 2:** To a solution of **15a** in ethyl alcohol (1.0 mL) was added hydrazine hydrate (242 μ mol, 14 μ L). The mixture was stirred at 80 °C for 1 hour. After such time the mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC according to one of the purification methods 3-1 to 3-4.

Purification Methods (PM)

[0441] **PM 3-1:** column: Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 5% - 25%, 11 min.

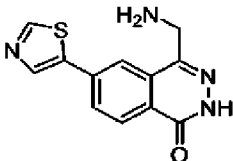
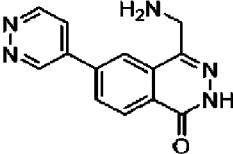
[0442] **PM 3-2:** column: Waters Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 12% - 42%, 10 min.

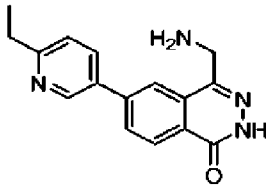
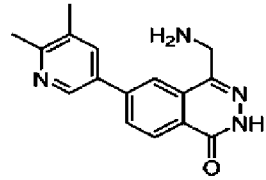
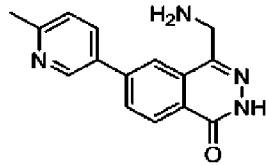
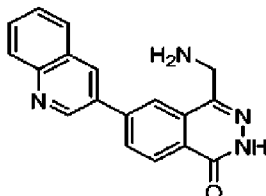
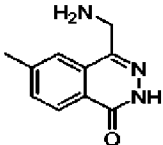
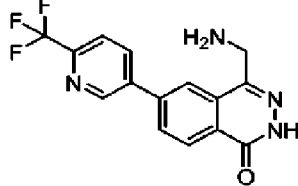
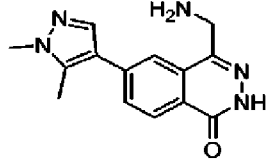
[0443] **PM 3-3:** column: Waters Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 2% - 32%, 10 min.

[0444] **PM 3-4:** column: Phenomenex Luna C18 75 $\times$ 10mm $\times$ 3 μ m; mobile phase:[water (0.05%HCl)-ACN]; B%: 11%-31%, 6.5 min.

[0445] Following the teachings of the General Reaction Schemes, the coupling methods 3A, 3B and 3C and using purification methods 3-1, 3-2, 3-3 and 3-4 and the Intermediates disclosed herein, the Examples **3-1** to **3-61** are prepared as shown in Table 3.

Table 3

Example	Structure	CM	PM	Compound Name and Characterization
3-1		3C	3-1	4-(aminomethyl)-6-(thiazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 259.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.97 (s, 1H), 9.27 (s, 1H), 8.71 (s, 1H), 8.59 (br s, 3H), 8.33 (d, J = 8.4 Hz, 1H), 8.27 - 8.24 (d, J = 1.6 Hz, 1H), 8.19 (dd, J = 1.6, 8.4 Hz, 1H), 4.59 - 4.50 (d, J = 5.6 Hz, 2H)
3-2		3B	3-1	4-(aminomethyl)-6-(pyridazin-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 253.26; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.06 (s, 1H), 9.97 (d, J = 1.2 Hz, 1H), 9.48 (d, J = 4.4 Hz, 1H), 8.68 (br s, 3H), 8.54 (s, 1H), 8.44 (m,

				2H), 8.42 (dd, J = 2.4, 5.2 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H)
3-3		3A	3-1	4-(aminomethyl)-6-(6-ethylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 281.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.33 (d, J = 2.0 Hz, 1H), 8.85 (br d, J = 7.6 Hz, 1H), 8.66 (br s, 3H), 8.43 (d, J = 1.2 Hz, 1H), 8.42 - 8.39 (m, 1H), 8.37 - 8.32 (m, 1H), 7.95 (br d, J = 8.4 Hz, 1H), 4.70 - 4.48 (m, 2H), 3.07 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H)
3-4		3A	3-3	4-(aminomethyl)-6-(5,6-dimethylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 281.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.72 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 4.12 (s, 2H), 2.52 (s, 3H), 2.39 (s, 3H)
3-5		3A	3-3	4-(aminomethyl)-6-(6-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 267.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.91 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.11 (dd, J = 2.0, 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 4.12 (s, 2H), 2.57 (s, 3H)
3-6		3A	3-2	4-(aminomethyl)-6-(quinolin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 303.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.55 (br s, 1H), 9.43 (d, J = 2.4 Hz, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.43 - 8.38 (m, 1H), 8.38 - 8.33 (m, 1H), 8.12 (dd, J = 4.8, 7.6 Hz, 2H), 7.84 (dt, J = 1.2, 7.6 Hz, 1H), 7.75 - 7.67 (m, 1H), 4.14 (s, 2H)
3-7		3A	3-1	4-(aminomethyl)-6-methylphthalazin-1(2H)-one LCMS [M+1] ⁺ = 189.21; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.39 (br s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.66 (dd, J = 0.8, 8.0 Hz, 1H), 3.98 (s, 2H), 2.52 (br s, 3H)
3-8		3A	3-1	4-(aminomethyl)-6-(6-(trifluoromethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 320.9; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 (s, 1H), 9.35 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 2.0, 8.4 Hz, 1H), 8.50 (br s, 3H), 8.46 - 8.41 (m, 1H), 8.40 (s, 1H), 8.38 - 8.34 (m, 1H), 8.13 (d, J = 8.0 Hz, 1H), 4.60 (br s, 2H)
3-9		3A	3-1	4-(aminomethyl)-6-(1,5-dimethyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.9 (s, 1H), 8.48 (br s, 3H), 8.29 (d, J = 8.4 Hz, 1H), 7.97 (dd, J = 1.6, 8.4 Hz, 1H), 7.90 (s, 2H), 4.52 (br d, J = 5.6 Hz, 2H), 3.83 (s, 3H), 2.52 (br s, 3H)

3-10		3A	3-1	4-(aminomethyl)-6-(5-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 267.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.0 (s, 1H), 9.18 (s, 1H), 8.71 (s, 1H), 8.59 (br s, 1H), 8.56 (br s, 3H), 8.45 - 8.39 (m, 1H), 8.38 (s, 1H), 8.36 - 8.32 (m, 1H), 4.59 (br d, J = 5.6 Hz, 2H), 2.54 - 2.52 (s, 3H)
3-11		3A	3-1	4-(aminomethyl)-6-(2-methylpyrimidin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 268.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.99 (s, 1H), 9.34 (s, 2H), 8.71 (br s, 3H), 8.43 - 8.30 (m, 3H), 4.56 (br d, J = 5.6 Hz, 2H), 2.73 (s, 3H)
3-12		3A	3-2	4-(aminomethyl)-6-(2-(trifluoromethyl)pyrimidin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 322.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.53 (s, 2H), 8.51 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.29 (dd, J = 1.6, 8.4 Hz, 1H), 4.13 (s, 2H)
3-13		3A	3-2	4-(aminomethyl)-6-(5-ethylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 281.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.86 (d, J = 2.0 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 1.6 Hz, 1H), 8.15 (dd, J = 2.0, 8.4 Hz, 1H), 8.06 (s, 1H), 4.13 (s, 2H), 2.77 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H)
3-14		3B	3-1	4-(aminomethyl)-6-(5-isopropylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 295.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 9.28 (br s, 1H), 8.82 (s, 1H), 8.79 - 8.74 (m, 1H), 8.65 (br s, 3H), 8.44 - 8.37 (m, 3H), 4.60 (q, J = 5.6 Hz, 2H), 3.25 - 3.17 (m, 1H), 1.37 (d, J = 7.2 Hz, 6H)
3-15		3A	3-1	4-(aminomethyl)-6-(1-ethyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.81 (s, 1H), 8.56 (m, 4H), 8.24 (d, J = 8.8 Hz, 1H), 8.20 (s, 1H), 8.14 - 8.09 (m, 2H), 4.48 (br d, J = 5.6 Hz, 2H), 4.19 (d, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H)
3-16		3A	3-1	4-(aminomethyl)-6-(pyrazolo[1,5-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 292.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.84 (d, J = 6.8 Hz, 1H), 8.74 (s, 1H), 8.59 (br s, 3H), 8.37 - 8.31 (m, 1H), 8.30 - 8.24 (m, 2H), 8.16 (d, J = 1.2 Hz, 1H), 7.48 (ddd, J = 1.2, 6.8, 9.2 Hz, 1H), 7.08 (dt, J = 1.2, 6.8 Hz, 1H), 4.61 (br s, 2H)
3-17		3A	3-2	4-(aminomethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 284.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.54 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 1.2 Hz, 1H), 8.13 (s, 1H), 8.06 (dd, J = 1.6, 8.4 Hz, 1H), 4.59 - 4.47 (m, 1H), 4.05 (s, 2H), 1.48 (d, J = 6.8 Hz, 6H)

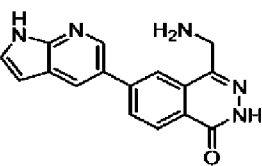
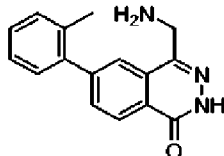
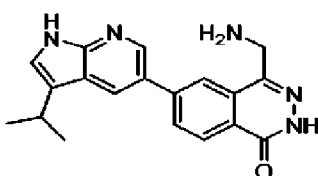
3-18		3A	3-2	4-(aminomethyl)-6-(2-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 267.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.53 (br s, 1H), 8.54 (dd, J = 1.6, 4.8 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 1.6 Hz, 1H), 7.88 (dd, J = 1.6, 8.0 Hz, 1H), 7.76 (dd, J = 1.6, 7.6 Hz, 1H), 7.38 (dd, J = 4.8, 7.6 Hz, 1H), 4.02 (s, 2H), 2.47 (s, 3H)
3-19		3A	3-3	4-(aminomethyl)-6-(4-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 267.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.52 - 8.49 (m, 2H), 8.36 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 1.2 Hz, 1H), 7.84 (dd, J = 1.6, 8.0 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 4.07 (s, 2H), 2.32 (s, 3H)
3-20		3A	3-2	4-(aminomethyl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 323.9; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.71 (br s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.08 (dd, J = 1.6, 8.4 Hz, 1H), 7.18 (s, 1H), 4.17 (s, 2H), 4.02 (s, 3H), 2.52 (br s, 2H)
3-21		3A	3-1	4-(aminomethyl)-6-(5-methyl-1H-pyrazol-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 256.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.55 (br s, 3H), 8.32 - 8.26 (m, 2H), 8.24 (s, 1H), 6.82 (d, J = 0.8 Hz, 1H), 4.60 - 4.43 (m, 2H), 2.37 - 2.22 (m, 3H)
3-22		3A	3-2	4-(aminomethyl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.43 (br s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 1.6, 8.4 Hz, 1H), 4.06 (s, 2H), 3.83 (s, 3H), 2.40 (s, 3H)
3-23		3A	3-2	4-(aminomethyl)-6-(1-propyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 284.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.49 - 12.35 (s, 1H), 8.49 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (s, 2H), 8.05 (dd, J = 1.6, 8.4 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H), 4.08 (s, 2H), 1.89 - 1.81 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H)
3-24		3A	3-1	4-(aminomethyl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 284.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.9 (s, 1H), 8.63 (br s, 3H), 8.31 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 1.2, 8.4 Hz, 1H), 7.76 (s, 1H), 4.46 (br d, J = 5.6 Hz, 2H), 3.76 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H)
3-25		3A	3-2	4-(aminomethyl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 324.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.52 (br s, 1H), 8.40 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.83 (br d, J = 8.8 Hz, 1H), 4.00 (s, 5H)

3-26		3A	3-1	4-(aminomethyl)-6-(1-isopentyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 312.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.59 (s, 4H), 8.26 - 8.20 (m, 2H), 8.14 (d, J = 1.6 Hz, 1H), 8.12 (s, 1H), 4.57 - 4.43 (m, 2H), 4.19 (t, J = 7.2 Hz, 2H), 1.81 - 1.69 (m, 2H), 1.52 (td, J = 6.8, 13.2 Hz, 1H), 0.93 (d, J = 6.4 Hz, 6H)
3-27		3A	3-1	4-(aminomethyl)-6-(1-isobutyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 296.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.9 - 12.8 (s, 1H), 8.49 (s, 1H), 8.44 - 8.36 (s, 3H), 8.25 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.13 (dd, J = 1.6, 8.4 Hz, 1H), 8.08 (s, 1H), 4.51 (q, J = 5.6 Hz, 2H), 3.98 (d, J = 7.2 Hz, 2H), 2.22 - 2.14 (m, 1H), 0.89 (d, J = 6.8 Hz, 6H).
3-28		3A	3-3	4-(aminomethyl)-6-(oxazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 243.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.51 (s, 1H), 8.35 (br s, 2H), 8.15 (br d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 4.09 (s, 2H).
3-29		3A	3-1	4-(aminomethyl)-6-(1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 306.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.57 (dd, J=1.6, 8.0 Hz, 1H), 8.51 (br s, 3H), 8.40 (dd, J=1.2, 4.4 Hz, 1H), 8.37 (s, 1H), 8.35 - 8.31 (m, 1H), 8.30 - 8.26 (m, 1H), 8.14 (d, J=1.2 Hz, 1H), 7.29 (dd, J=4.8, 8.0 Hz, 1H), 4.61 (br d, J=5.6 Hz, 2H), 3.94 (s, 3H)
3-30		3A	3-1	4-(aminomethyl)-6-(1-methyl-1H-imidazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 256.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 9.15 (s, 1H), 8.62 - 8.53 (br s, 3H), 8.43 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 1.2 Hz, 1H), 8.14 (dd, J = 1.6, 8.4 Hz, 1H), 8.07 (s, 1H), 4.54 - 4.47 (m, 2H), 3.95 (s, 3H)
3-31		3A	3-1	4-(aminomethyl)-6-(1H-imidazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 242.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.99 (s, 1H), 9.11 (br s, 1H), 8.62 (s, 1H), 8.58 (br s, 3H), 8.46 (s, 1H), 8.38 (m, 2H), 4.53 (br s, 2H)
3-32		3A	3-1	4-(aminomethyl)-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 286.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.53 - 8.49 (s, 1H), 8.46 (br s, 3H), 8.27 - 8.19 (m, 2H), 8.16 - 8.11 (m, 1H), 8.09 (s, 1H), 4.55 - 4.47 (m, 2H), 4.20 (br t, J = 5.6 Hz, 2H), 3.79 (br t, J = 5.6 Hz, 2H)
3-33		3C	3-1	4-(aminomethyl)-6-(5-cyclopropylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 293.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 (s, 1H), 9.32 (d, J = 2.0 Hz, 1H), 8.86 - 8.69 (m, 4H), 8.65 (s, 1H), 8.48 (s, 1H), 8.40 (s, 2H), 4.59 (br d, J = 5.6 Hz, 2H), 2.36 - 2.25 (m, 1H), 1.29 - 1.03 (m, 4H)

3-34		3A	3-1	4-(aminomethyl)-6-(5-propylpyridin-3-yl)phthalazin-1(2H)-one ¹ H NMR (400 MHz, MeOD) δ = 8.82 (s, 1H), 8.51 - 8.47 (m, 2H), 8.24 (s, 1H), 8.20 - 8.13 (m, 2H), 4.27 (s, 2H), 2.78 (t, J = 7.6 Hz, 2H), 1.02 (t, J = 7.6 Hz, 3H)
3-35		3A	3-2	4-(aminomethyl)-6-(5-(cyclopropylmethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ 307.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.76 - 12.38 (m, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.39 - 8.32 (m, 2H), 8.23 - 8.19 (m, 1H), 8.17 (t, J = 2.0 Hz, 1H), 4.17 (s, 2H), 2.64 (d, J = 6.8 Hz, 2H), 1.14 - 1.04 (m, 1H), 0.55 - 0.48 (m, 2H), 0.33 - 0.26 (m, 2H)
3-36		3B	3-2	4-(aminomethyl)-6-(5-(difluoromethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ 303.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.26 - 9.18 (m, 1H), 8.87 (d, J = 1.6 Hz, 1H), 8.44 - 8.36 (m, 3H), 8.22 - 8.18 (m, 1H), 7.36 - 7.07 (m, 1H), 4.14 (s, 2H)
3-37		3B	3-3	5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)nicotinonitrile LCMS [M+1] ⁺ 278.0 ¹ H NMR (400MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.46 (d, J = 2.4 Hz, 1H), 9.14 (d, J = 2.0 Hz, 1H), 8.97 (t, J = 2.0 Hz, 1H), 8.62 (br s, 3H), 8.42 - 8.39 (m, 2H), 8.38 - 8.34 (m, 1H), 4.57 (q, J = 5.6 Hz, 2H)
3-39		3A	3-1	4-(aminomethyl)-6-(5-(prop-1-yn-1-yl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ 291.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.55 (s, 1H), 9.02 (d, J = 2.4 Hz, 1H), 8.67 (d, J = 1.6 Hz, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.36 - 8.32 (m, 2H), 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 4.12 (s, 2H), 2.13 (s, 3H)
3-40		3A	4-3	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)benzonitrile LCMS [M+1] ⁺ 354.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.35 (d, J = 2.0 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.74 (t, J = 2.0 Hz, 1H), 8.63 (br s, 3H), 8.46 - 8.40 (m, 3H), 8.08 (d, J = 7.6 Hz, 1H), 7.93 - 7.87 (m, 2H), 7.75 - 7.68 (m, 1H), 4.63 - 4.53 (m, 2H)
3-41		3A	3-1	4-(aminomethyl)-6-(5-fluoropyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ 271.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.0 (s, 1H), 9.08 (t, J = 1.6 Hz, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.51 (br s, 3H), 8.42 (m, 2H), 8.37 - 8.34 (m, 2H), 4.63 - 4.57 (m, 2H)
3-42		3A	3-1	4-(aminomethyl)-6-(5-chloropyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ 287.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.6 (br s, 1H), 9.06 (d, J = 2.0 Hz, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.51 (t, J = 2.0 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.24 (dd, J = 1.6, 8.4 Hz, 1H), 4.10 (s, 2H), 2.31 - 1.93 (br s, 2H)

3-43		3A	4-3	4-(aminomethyl)-6-(5-(trifluoromethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 321.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 9.47 (d, J = 2.4 Hz, 1H), 9.12 - 9.10 (s, 1H), 8.79 (s, 1H), 8.50 (br s, 3H), 8.42 - 8.39 (m, 3H), 4.64 - 4.58 (m, 2H)
3-44		3A	3-1	4-(aminomethyl)-6-(5-hydroxypyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 269.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 11.61 (s, 1H), 8.91 (d, J = 1.2 Hz, 1H), 8.61 (br s, 3H), 8.47 (d, J = 2.4 Hz, 1H), 8.42 - 8.36 (m, 2H), 8.29 (dd, J = 1.6, 8.0 Hz, 1H), 8.24 (br s, 1H), 4.58 (br d, J = 5.6 Hz, 2H)
3-45		3A	3-1	4-(aminomethyl)-6-(5-methoxypyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 282.9 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 8.95 (d, J = 1.6 Hz, 1H), 8.67 (br s, 3H), 8.57 (d, J = 2.8 Hz, 1H), 8.42 - 8.34 (m, 3H), 8.28 (s, 1H), 4.69 - 4.44 (m, 2H), 4.03 (s, 3H)
3-46		3A	3-1	4-(aminomethyl)-6-(5-(methoxymethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 297.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.54 (br s, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.38 - 8.34 (m, 2H), 8.23 - 8.18 (m, 2H), 4.57 (s, 2H), 4.11 (s, 2H), 3.37 (s, 3H), 2.30 - 1.93 (m, 2H)
3-47		3A	3-2	4-(aminomethyl)-6-(5-(hydroxymethyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 283.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.48 - 12.06 (m, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 1.2 Hz, 1H), 8.16 - 8.12 (m, 2H), 5.15 (br s, 1H), 4.68 (s, 2H), 4.13 (s, 2H)
3-48		3A	3-2	4-(aminomethyl)-6-(5-(methylsulfonyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 331.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 9.49 (d, J = 2.0 Hz, 1H), 9.17 (d, J = 2.0 Hz, 1H), 8.84 (t, J = 2.0 Hz, 1H), 8.61 (br s, 3H), 8.46 - 8.37 (m, 3H), 4.60 (s, 2H), 3.46 (s, 3H)
3-49		3A	3-1	4-(aminomethyl)-6-(5-ethoxypyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 297.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 8.97 (d, J = 1.6 Hz, 1H), 8.68 (br s, 3H), 8.58 (d, J = 2.8 Hz, 1H), 8.43 - 8.35 (m, 3H), 8.33 (s, 1H), 4.71 - 4.53 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H)
3-50		3A	3-1	4-(aminomethyl)-6-(5-phenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 345.1 ¹ H NMR (400 MHz, MeOH-d ₄) δ = 8.91 (s, 1H), 8.54 (d, J = 9.2 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.26 - 8.22 (m, 2H), 8.19 (t, J = 2.0 Hz, 1H), 7.52 - 7.47 (m, 2H), 7.31 - 7.26 (m, 1H), 7.23 - 7.19 (m, 2H), 4.69 (s, 2H)

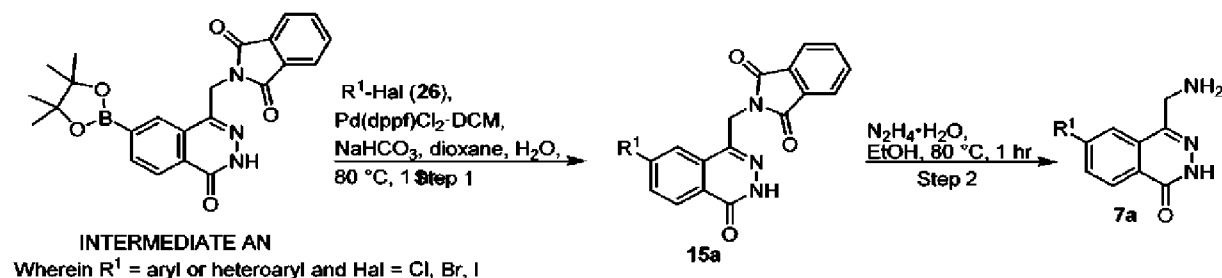
3-51		3B	3-1	4-(aminomethyl)-6-(5-(difluoromethoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 318.9 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.08 (d, J = 2.0 Hz, 1H), 8.63 (br d, J = 2.8 Hz, 4H), 8.42 - 8.36 (m, 2H), 8.35 - 8.30 (m, 2H), 7.77 - 7.31 (d, J = 73.2 Hz, 1H), 4.67 - 4.47 (m, 2H)
3-52		3A	3-2	4-(aminomethyl)-6-(5-isopropoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 311.2 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.54 (br s, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.38 - 8.27 (m, 3H), 8.19 (dd, J = 1.6, 8.4 Hz, 1H), 7.81 (t, J = 2.4 Hz, 1H), 4.90 (spt, J = 6.0 Hz, 1H), 4.10 (s, 2H), 1.33 (d, J = 6.0 Hz, 6H).
3-53		3A	3-1	4-(aminomethyl)-6-(5-(cyclopropylmethoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 323.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.00 (d, J = 1.6 Hz, 1H), 8.72 (br s, 3H), 8.59 (d, J = 2.4 Hz, 1H), 8.46 - 8.29 (m, 4H), 4.62 - 4.56 (m, 2H), 4.15 (d, J = 7.2 Hz, 2H), 1.40 - 1.16 (m, 1H), 0.76 - 0.56 (m, 2H), 0.45 - 0.29 (m, 2H)
3-54		3A	3-1	4-(aminomethyl)-6-(isoquinolin-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 303.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 9.85 (s, 1H), 8.82 (s, 1H), 8.66 (br s, 3H), 8.57 (d, J = 8.4 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 1.0 Hz, 1H), 8.19 - 7.93 (m, 4H), 4.51 (br d, J = 5.6 Hz, 2H)
3-55		3A	3-1	4-(aminomethyl)-6-(1H-pyrrolo[2,3-c]pyridin-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 292.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.46 (br s, 1H), 13.05 (s, 1H), 9.27 (s, 1H), 8.77 (s, 1H), 8.67 (br s, 3H), 8.53 - 8.42 (m, 2H), 8.40 - 8.31 (m, 2H), 7.21 (br s, 1H), 4.60 (br d, J = 4.4 Hz, 2H)
3-56		3A	3-1	4-(aminomethyl)-6-(5-chloro-4-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 301.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 - 13.00 (s, 1H), 8.71 (s, 1H), 8.59 - 8.44 (m, 4H), 8.39 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.99 (dd, J = 1.6, 8.4 Hz, 1H), 4.54 - 4.45 (m, 2H), 2.33 (s, 3H)
3-57		3A	3-1	4-(aminomethyl)-6-(4-benzyl-4H-1,2,4-triazol-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 333.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 9.05 (s, 1H), 8.59 (br s, 3H), 8.37 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 8.14 (dd, J = 1.6, 8.4 Hz, 1H), 7.35 - 7.23 (m, 3H), 7.10 - 7.05 (m, 2H), 5.56 (s, 2H), 4.47 - 4.35 (m, 2H).
3-58		3A	3-1	4-(aminomethyl)-6-(5-morpholinopyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 338.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 8.71 (s, 1H), 8.53 (br s, 3H), 8.49 (d, J = 2.8 Hz, 1H), 8.43 - 8.39 (d, J = 8.4 Hz, 1H), 8.38 - 8.34 (dd, J = 1.6, 8.4 Hz, 1H), 8.34 (s, 1H), 8.17 - 8.07 (s, 1H), 4.61 (q, J = 6.0 Hz, 2H), 3.83 - 3.79 (t, J = 4.8 Hz, 4H), 3.47 - 3.45 (m, 4H)

3-59		3A	3-2	4-(aminomethyl)-6-(1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 292.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.6 (br s, 1H), 11.85 (br s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.37 - 8.31 (m, 2H), 8.27 - 8.17 (m, 1H), 7.57 (dd, J = 2.0, 3.2 Hz, 1H), 6.60 - 6.54 (m, 1H), 4.20 (s, 2H), 3.88 - 3.54 (s, 2H)
3-60		3A	3-1	4-(aminomethyl)-6-(o-tolyl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 266.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.0 (s, 1H), 8.39 - 8.33 (m, 4H), 7.94 - 7.90 (m, 2H), 7.40 - 7.34 (m, 4H), 4.51 (s, 2H), 2.28 (s, 3H)
3-61		3A	3-4	4-(aminomethyl)-6-(3-isopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 334.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.94 (s, 1H), 11.80 (br s, 1H), 8.83 (d, J = 2.0 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.60 (br s, 3H), 8.41 - 8.36 (m, 1H), 8.36 - 8.31 (m, 1H), 8.29 (s, 1H), 7.36 (d, J = 2.0 Hz, 1H), 4.63 (br d, J = 5.6 Hz, 2H), 3.36 - 3.19 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H)

EXAMPLES 4-1 to 4-180

COUPLING METHODS (CM) AND PURIFICATION METHODS (PM) FOR THE PREPARATION OF EXAMPLES IN TABLE 4

CM 4A:

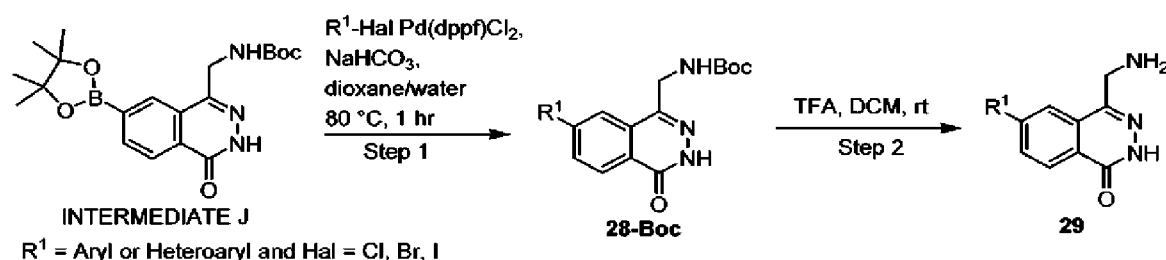


[0446] **Step 1:** A mixture of the appropriate aryl/heteroaryl-halide **26** (390 μmol, 1.5 *eq.*), intermediate AN (260 μmol, 1.00 *eq.*), Pd(dppf)Cl₂ (26 μmol, 0.10 *eq.*), sodium bicarbonate (43.7 mg, 521 μmol, 20.3 μL, 2.00 *eq.*) in dioxane (1.0 mL) and water (0.2 mL) was purged with nitrogen 3 times. The mixture was then stirred at 80 °C for 2 hours. After such time the mixture was filtered, washed with a dichloromethane: methyl alcohol 10: 1 mixture and the filtrate concentrated under reduced pressure to give a residue. This concentrated residue was

trituted with methyl alcohol (3.0 mL), filtered and dried to give the corresponding coupling product **15a** as a black solid.

[0447] **Step 2:** To a solution of corresponding coupling product **15a** in ethyl alcohol (1.00 mL) was added hydrazine hydrate (242 μ mol, 14 μ L). The mixture was stirred at 80 °C for 1 hour. After such time the mixture was concentrated in vacuo and the residue purified by prep-HPLC according to one of the purification methods 4-1 to 4-13.

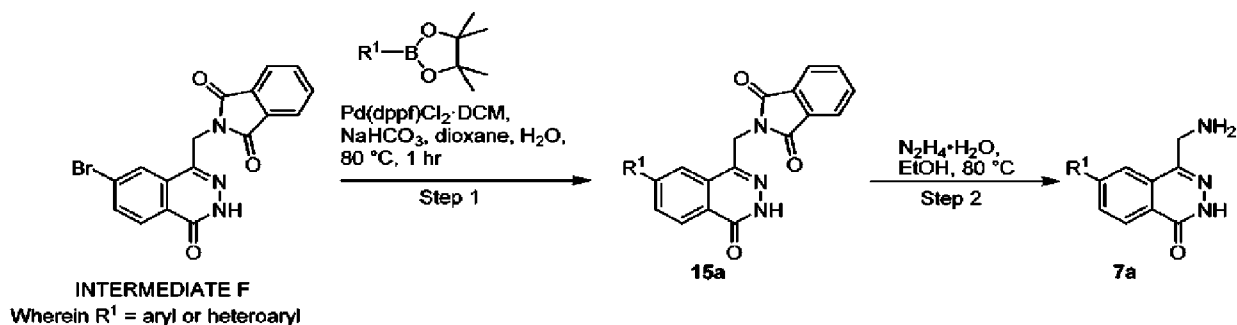
CM 4B:



[0448] **Step 1:** Intermediate J (189 mg, 470 μ mol, 1.00 *eq.*), aryl/heteroaryl-halide **26** (564 μ mol, 1.20 *eq.*), Pd(dppf)Cl₂ (34 mg, 47 μ mol, 0.10 *eq.*), sodium bicarbonate (79 mg, 940 μ mol, 37 μ L, 2.00 *eq.*) in dioxane (1 mL) and water (0.20 mL) was purged with nitrogen 3 times, and stirred at 80 °C for 2 hours. Upon completion, the reaction mixture was poured into water (40 mL), filtered and the filter cake was dried under reduced pressure to give R²-Pyridyl-Suzuki coupling product **28-Boc** (71 mg, crude) as a gray solid and used into the next step directly without further purification.

[0449] **Step 2:** To a solution of *tert*-butyl *N*-[[4-oxo-7-(5-pyrimidin-2-yloxy-3-pyridyl)-3*H*-phthalazin-1-yl]methyl]carbamate R²-Pyridyl-Suzuki coupling product **28-Boc** (60 mg, crude) in dichloromethane (1 mL) was added trifluoroacetic acid (462 mg, 4.05 mmol, 0.30 mL). The mixture was stirred at 30 °C for 0.5 hour and upon completion concentrated to a residue under reduced pressure. The concentrated residue **29** was purified by prep-HPLC according to one of the purification methods 4-1 through 4-13.

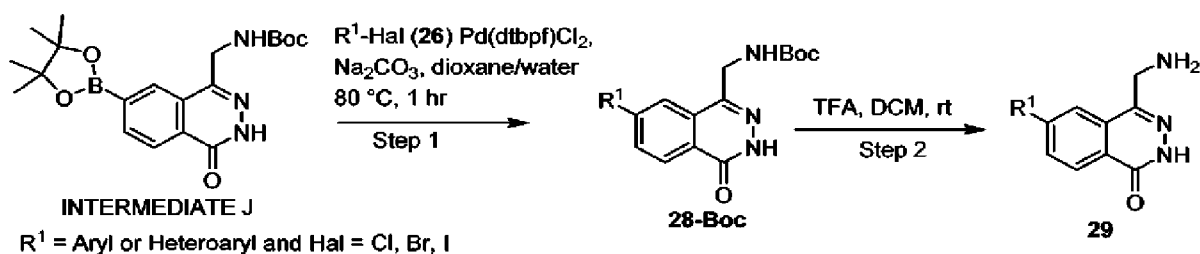
CM 4C



[0450] **Step 1:** A mixture of the appropriate aryl/heteroaryl boronic ester (303 μmol , 1.16 eq.), intermediate F (100 mg, 260 μmol , 1.00 eq.), Pd(dppf)Cl_2 (19 mg, 26 μmol , 0.10 eq.), sodium bicarbonate (66 mg, 781 μmol , 30 μL , 3.00 eq.) in dioxane (1 mL) and water (0.20 mL) was degassed and purged with nitrogen 3 times and stirred at 80°C for 1 hour under a nitrogen atmosphere. After such time the mixture was filtered and concentrated under reduced pressure to give a residue. The concentrated residue was purified by column chromatography (SiO_2 , petroleum ether: ethyl acetate 10:1 to 0:1) to give the corresponding Suzuki coupling product **15a** (12.0 mg, crude) as a yellow solid.

[0451] **Step 2:** To a solution of corresponding Suzuki coupling product **15a** (10 mg, crude), in ethyl alcohol (1.0 mL) was added hydrazine hydrate (10 mg, 207 μmol , 10 μL). The mixture was stirred at 80°C for 1 hour, cooled and concentrated under reduced pressure. The concentrated residue **7a** was then purified by prep-HPLC according to one of the purification methods 4-1 to 4-13 described herein.

CM 4D

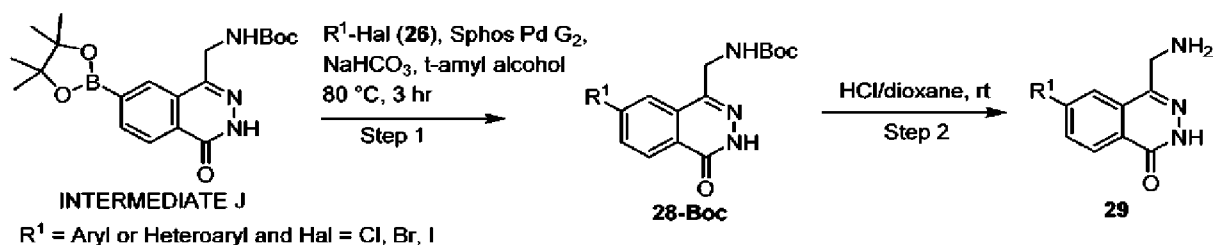


[0452] **Step 1:** Intermediate J (69 mg, 17 μmol , 1.30 eq.), aryl/heteroaryl-halide **26** (132 μmol , 1.0 eq.), Pd(dtbpf)Cl_2 (9 mg, 13 μmol , 0.10 eq.), sodium carbonate (28 mg, 263 μmol ,

2.00 *eq.*) in dioxane (1.5 mL) and water (0.30 mL) was purged with nitrogen 3 times, and stirred at 80 °C for 2 hours. After such time the mixture was concentrated and the residue purified by prep-TLC (SiO₂, CH₂Cl₂: MeOH 20:1) to give R¹-Suzuki coupling product **28-Boc** and used into the next step directly without further purification.

[0453] **Step 2:** To a solution of *tert*-butyl *N*-[[4-oxo-7-(R¹)-3*H*-phthalazin-1-yl]methyl]carbamate Suzuki coupling product **28-Boc** (40 mg) in dichloromethane (1.5 mL) was added trifluoroacetic acid (5.4 mmol, 0.4 mL). The mixture was stirred at 25 °C for 0.5 hour and upon completion concentrated to a residue under reduced pressure. The concentrated residue **29** was purified by prep-HPLC according to one of the purification methods 4-1 through 4-13.

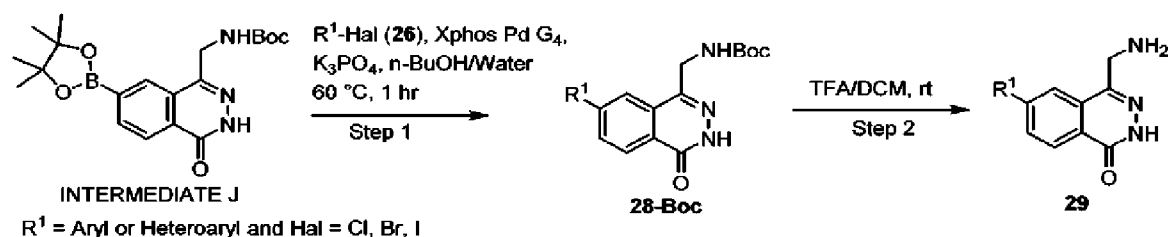
CM 4E



[0454] **Step 1:** Intermediate J (80 mg, 0.20 mmol, 1.00 *eq.*), aryl/heteroaryl-halide **26** (239 μmol, 1.2 *eq.*), [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (14.4 mg, 19.9 μmol, 0.10 *eq.*), sodium bicarbonate (34 mg, 398 μmol, 2.00 *eq.*) in 2-methyl-2-butanol (2.00 mL) and water (0.4 mL) was purged with nitrogen 3 times, and stirred at 80 °C for 3 hours. After such time the mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL × 3) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was then purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate = 1: 1.5) to give R¹-Suzuki coupling product **28-Boc** which was used in the next.

[0455] **Step 2:** A solution of *tert*-butyl *N*-[[4-oxo-7-(R¹)-3*H*-phthalazin-1-yl]methyl]carbamate Suzuki coupling product **28-Boc** (0.08 mmol, 1.00 *eq.*) in HCl•dioxane (2.00 mL, 101 *eq.*) was stirred at 25 °C for 12 hours. The reaction was concentrated in vacuo and the residue purified by prep-HPLC according to one of the purification methods 4-1 through 4-13.

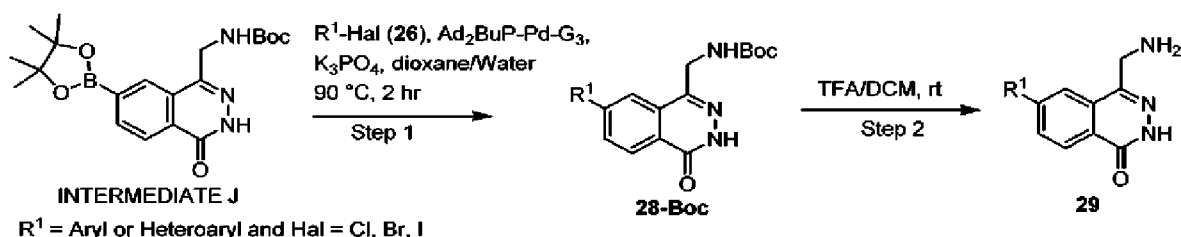
CM 4F:



[0456] **Step 1:** Intermediate J (80 mg, 0.20 mmol, 1.00 *eq.*), aryl/heteroaryl-halide 26 (0.24 mmol, 1.2 *eq.*), methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II) (20 μ mol, 0.10 *eq.*), potassium phosphate, 0.40 mmol, 2.00 *eq.*) in *n*-butanol (2.0 mL) and water (0.4 mL) was purged with nitrogen 3 times, and stirred at 60 °C for 1 hour. After such time the mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL $\times$ 3) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was then purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 20%) to give R^1 -Suzuki coupling product **28-Boc** which was used in the next step.

[0457] **Step 2:** To a solution of *tert*-butyl *N*-[[4-oxo-7-(R^1)-3*H*-phthalazin-1-yl]methyl]carbamate Suzuki coupling product **28-Boc** (40.0 mg) in dichloromethane (1.5 mL) was added trifluoroacetic acid (5.4 mmol, 0.40 mL). The mixture was stirred at 25 °C for 0.5 hour and upon completion concentrated to a residue under reduced pressure. The concentrated residue **29** was purified by prep-HPLC according to one of the purification methods 4-1 through 4-13.

CM 4G:



[0458] **Step 1:** Intermediate J (40 mg, 0.10 mmol, 1.25 *eq.*), aryl/heteroaryl-halide 26 (0.076 mmol, 1.0 *eq.*), [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane methanesulfonate (8 μ mol, 0.10 *eq.*), potassium phosphate, (0.23 mmol, 3.00 *eq.*) in dioxane (1.5 mL) and water (0.3 mL) was purged with nitrogen 3 times, and stirred at 90 °C for 2

hours. After such time the mixture was filtered, concentrated and the residue was then purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 60%) to give R¹-Suzuki coupling product **28-Boc** which was used in the next step.

[0459] **Step 2:** To a solution of *tert*-butyl *N*-[[4-oxo-7-(R¹)-3*H*-phthalazin-1-yl]methyl]carbamate Suzuki coupling product **28-Boc** (30.0 mg) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.2 mL). The mixture was stirred at 25 °C for 0.5 hour and upon completion concentrated to a residue under reduced pressure. The concentrated residue **29** was purified by prep-HPLC according to one of the purification methods 4-1 through 4-13.

Purification Methods (PM)

[0460] **PM 4-1:** column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 5%-30%, 10 min.

[0461] **PM 4-2:** column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 5%-40%, 10 min.

[0462] **PM 4-3:** column: Waters Atlantis T3 150 × 30 mm × 5 μm; mobile phase: [water (0.225% FA)-ACN]; B%: 1%-20%, 10 min.

[0463] **PM 4-4:** column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 1%-30%, 10 min.

[0464] **PM 4-5:** column: Phenomenex Gemini NX-C18 75 × 30 mm × 3 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 5%-40%, 7 min.

[0465] **PM 4-6:** column: Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 10%-35%, 6.5 min.

[0466] **PM 4-7:** column: Xtimate C18 150 × 40 mm × 10 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 5%-35%, 10 min.

[0467] **PM 4-8:** column: Waters Xbridge BEH C18 150 × 25 mm × 5 μm; mobile phase: [water (0.05% NH₄HCO₃ v/v)-ACN]; B%: 5%-40%, 10 min.

[0468] **PM 4-9:** column: Nano-micro Kromasil C18 100 mm × 40 mm × 10 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 1%-40%, 8 min.

[0469] **PM 4-10:** SFC (column: Daicel ChiralPak IG (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH₃H₂O/MeOH]; B%: 40% isocratic, 7.8 min; 109 min).

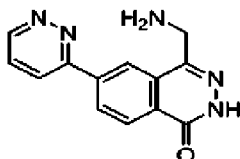
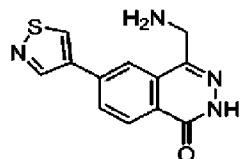
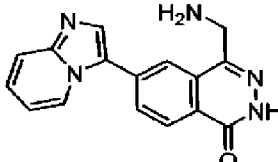
[0470] **PM 4-11:** SFC (column: Phenomenex-Cellulose-2 (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH₃H₂O/MeOH]; B%: 50% isocratic, 11.0 min; 95 min).

[0471] **PM-4-12:** The residue was diluted with 50% sodium bicarbonate (20 mL) and extracted with dichloromethane (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give title compound.

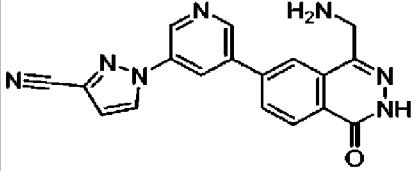
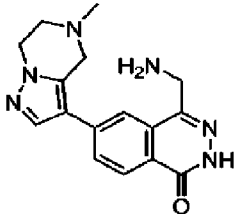
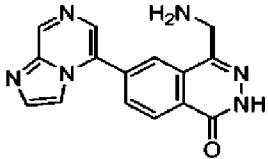
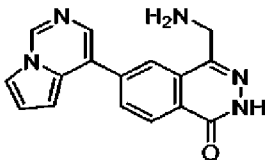
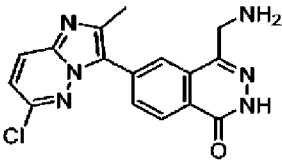
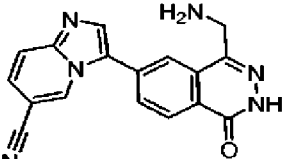
[0472] **PM 4-13:** column: Welch Xtimate C18 150 mm × 25 mm × 5 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 10%-40%, 8 min.

[0473] Following the teachings of the General Reaction Schemes, the coupling methods 4A-G, and using purification methods 4-1 to 4-13 and the Intermediates disclosed herein, the Examples 4-1 to 4-252 are prepared as shown in Table 4:

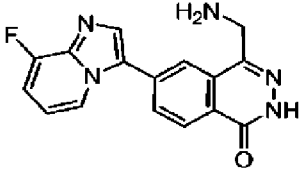
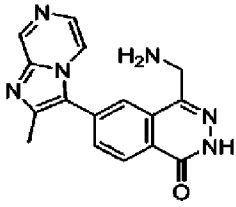
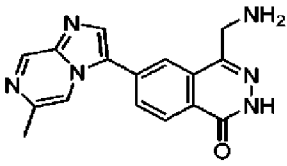
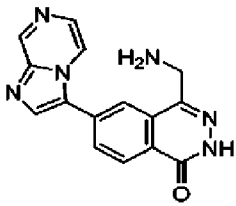
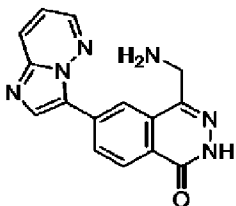
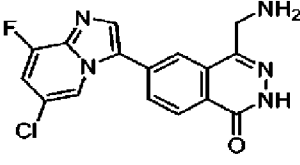
Table 4

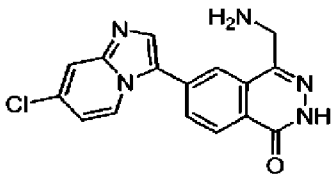
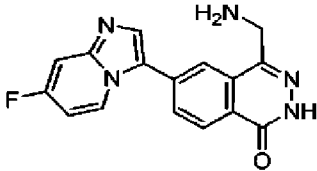
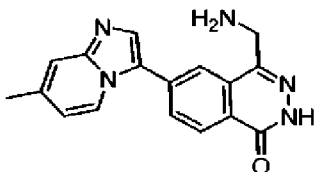
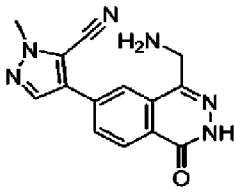
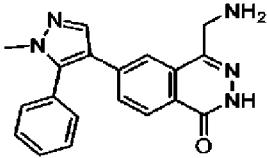
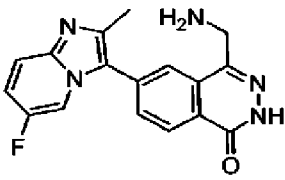
Example	Structure	CM	PM	Compound Name and Characterization
4-1		4A	4-1	4-(aminomethyl)-6-(pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 254.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 (s, 1H), 9.35 (dd, J = 1.6, 5.2 Hz, 1H), 8.71 (dd, J = 1.6, 8.4 Hz, 1H), 8.65 (d, J = 1.2 Hz, 1H), 8.62 (br dd, J = 1.6, 8.8 Hz, 4H), 8.46 (d, J = 8.4 Hz, 1H), 7.95 (dd, J = 4.8, 8.8 Hz, 1H), 4.61 (q, J = 5.2 Hz, 2H)
4-2		4A	4-1	4-(aminomethyl)-6-(isothiazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 258.8; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.96 (s, 1H), 9.76 (s, 1H), 9.35 (s, 1H), 8.52 (br s, 3H), 8.39 - 8.34 (m, 3H), 4.56 (br d, J = 5.6 Hz, 2H)
4-3		4A	4-1	4-(aminomethyl)-6-(imidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 292.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 9.14 (d, J = 6.8 Hz, 1H), 8.80 - 8.60 (m, 4H), 8.51 - 8.39 (m, 2H), 8.24 (dd, J = 1.2, 8.4 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 8.03 - 7.92 (m, 1H), 7.50 (t, J = 6.4 Hz, 1H), 4.53 (br d, J = 5.6 Hz, 2H)

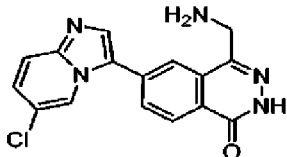
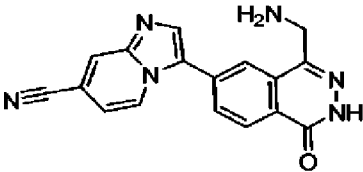
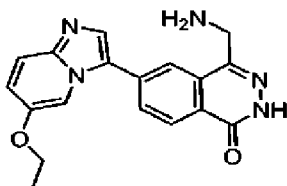
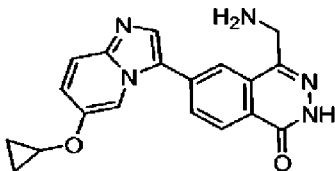
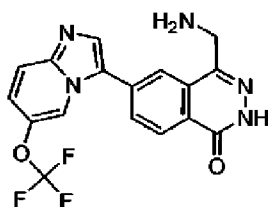
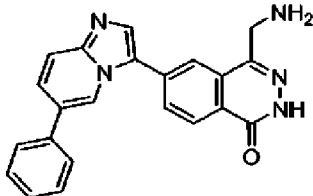
4-4		4A	4-1	4-(aminomethyl)-6-(1,2-dimethyl-1H-imidazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 270.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.07 (s, 1H), 8.69 (br s, 3H), 8.43 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 8.08 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (s, 1H), 4.49 (br d, J = 4.8 Hz, 2H), 3.79 (s, 3H), 2.72 (s, 3H)
4-5		4A	4-2	4-(aminomethyl)-6-(5-cyclopropyl-4-methylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 307.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.37 - 8.28 (m, 3H), 8.05 (d, J = 1.2 Hz, 1H), 7.80 (dd, J = 1.6, 8.0 Hz, 1H), 4.05 (s, 2H), 2.35 (s, 3H), 2.02 - 1.94 (m, 1H), 1.08 - 1.00 (m, 2H), 0.81 - 0.72 (m, 2H)
4-6		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-(difluoromethoxy)benzonitrile LCMS [M+1] ⁺ = 479.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.48 (br s, 3H), 8.29 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.81 - 7.39 (m, 4H), 7.21 (d, J = 2.0 Hz, 1H), 4.39 - 4.13 (m, 3H), 3.75 (s, 3H), 0.98 - 0.70 (m, 4H).
4-7		4A	4-1	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)picolinonitrile LCMS [M+1] ⁺ = 278.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 8.88 (dd, J = 1.2, 4.4 Hz, 1H), 8.57 (br s, 3H), 8.45 (d, J = 8.4 Hz, 1H), 8.37 - 8.31 (m, 2H), 8.23 (dd, J = 1.6, 8.0 Hz, 1H), 7.95 (dd, J = 4.8, 8.0 Hz, 1H), 4.52 - 4.45 (m, 2H)
4-8		4A	4-1	4-(5-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-1-methyl-1H-pyrazole-5-carbonitrile LCMS [M+1] ⁺ = 358.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 9.19 (d, J = 2.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.58 (t, J = 2.0 Hz, 1H), 8.50 - 8.42 (m, 4H), 8.39 - 8.33 (m, 3H), 4.67 - 4.55 (s, 2H), 4.13 (s, 3H)
4-9		4A	4-1	4-(aminomethyl)-6-(5-(trifluoromethoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 337.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.25 (d, J = 2.0 Hz, 1H), 8.82 (d, J = 1.6 Hz, 1H), 8.65 - 8.49 (m, 4H), 8.42 - 8.38 (m, 1H), 8.38 - 8.33 (m, 2H), 4.65 - 4.54 (m, 2H)

4-10		4A	4-2	1-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-1H-pyrazole-3-carbonitrile LCMS [M+1] ⁺ = 344.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.65 - 12.51 (m, 1H), 9.23 (d, J = 2.4 Hz, 1H), 9.18 (d, J = 2.0 Hz, 1H), 9.02 (d, J = 2.8 Hz, 1H), 8.76 (t, J = 2.0 Hz, 1H), 8.48 (s, 1H), 8.41 - 8.37 (m, 1H), 8.35 - 8.30 (m, 1H), 7.40 (d, J = 2.4 Hz, 1H), 4.13 (s, 2H)
4-11		4A	4-1	4-(aminomethyl)-6-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 311.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.91 (s, 1H), 12.28 (br s, 1H), 8.57 (br s, 3H), 8.36 - 8.23 (m, 2H), 7.98 - 7.84 (m, 2H), 4.84 (br s, 2H), 4.54 (br d, J = 4.0 Hz, 4H), 3.74 (br s, 2H), 2.99 (br s, 3H)
4-12		4A	4-1	4-(aminomethyl)-6-(imidazo[1,2-a]pyrazin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 293.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.12 (s, 1H), 9.29 - 9.23 (s, 1H), 8.52 (br s, 3H), 8.49 (s, 1H), 8.46 (d, J = 1.2 Hz, 1H), 8.39 (s, 1H), 8.33 (dd, J = 1.6, 8.4 Hz, 1H), 8.23 (s, 1H), 8.04 - 8.01 (m, 1H), 4.59 - 4.51 (d, J = 5.6 Hz, 2H)
4-13		4A	4-1	4-(aminomethyl)-6-(pyrrolo[1,2-c]pyrimidin-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 292.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.41 (s, 1H), 8.62 (br s, 3H), 8.42 (d, J = 8.4 Hz, 1H), 8.30 - 8.25 (m, 2H), 7.90 (dd, J = 1.2, 2.8 Hz, 1H), 7.78 (s, 1H), 7.06 (dd, J = 2.8, 3.6 Hz, 1H), 6.83 (d, J = 3.6 Hz, 1H), 4.57 (q, J = 5.4 Hz, 2H)
4-14		4A	4-1	4-(aminomethyl)-6-(6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 341.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 8.62 (br s, 3H), 8.45 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.6 Hz, 1H), 8.29 - 8.22 (m, 2H), 7.56 (d, J = 9.2 Hz, 1H), 4.47 (br d, J = 5.6 Hz, 2H), 2.61 (s, 3H)
4-15		4A	4-2	3-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)imidazo[1,2-a]pyridine-6-carbonitrile LCMS [M+1] ⁺ = 317.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.56 (s, 1H), 9.53 - 9.43 (m, 1H), 8.42 - 8.36 (m, 2H), 8.23 - 8.12 (m, 2H), 7.88 (dd, J = 0.8, 9.2 Hz, 1H), 7.63 (dd, J = 1.2, 9.2 Hz, 1H), 4.10 (s, 2H)

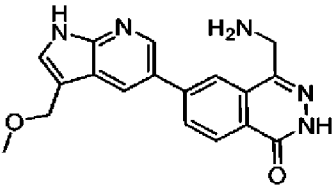
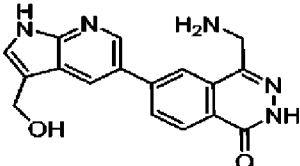
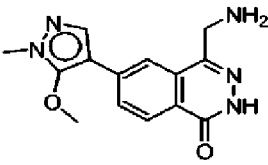
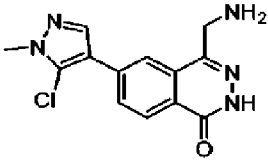
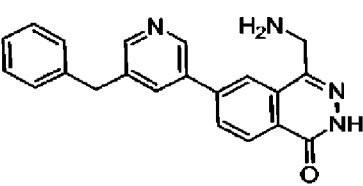
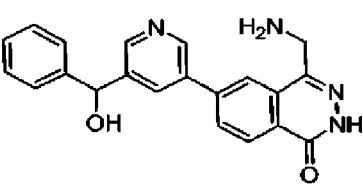
4-16		4A	4-2	4-(aminomethyl)-6-(6-methoxyimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 322.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.51 (br s, 1H), 8.47 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.65 (d, J = 10.0 Hz, 1H), 7.17 (dd, J = 2.0, 9.6 Hz, 1H), 4.07 (s, 2H), 3.83 (s, 3H)
4-17		4A	4-1	4-(aminomethyl)-6-(6-methylimidazo[1,2-b]pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 307.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.98 (s, 1H), 8.87 (s, 1H), 8.75 (dd, J = 1.2, 8.4 Hz, 1H), 8.71 (d, J = 1.2 Hz, 1H), 8.69 (br s, 3H), 8.42 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 9.6 Hz, 1H), 7.58 (d, J = 9.6 Hz, 1H), 4.58 - 4.51 (m, 2H), 2.71 (s, 3H).
4-18		4A	4-1	4-(aminomethyl)-6-(6-chloroimidazo[1,2-b]pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 327.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.97 (s, 1H), 8.74 (s, 1H), 8.71 - 8.61 (m, 4H), 8.59 (d, J = 1.2 Hz, 1H), 8.42 (m, 2H), 7.58 (d, J = 9.6 Hz, 1H), 4.59 - 4.47 (s, 2H).
4-19		4A	4-2	4-(aminomethyl)-6-(7-methoxyimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 322.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.57 (br s, 1H), 8.72 (d, J = 7.6 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.34 (d, J = 1.2 Hz, 1H), 8.14 (dd, J = 1.6, 8.4 Hz, 1H), 7.95 (s, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 2.8, 7.6 Hz, 1H), 4.14 (s, 2H), 3.95 (s, 3H)
4-20		4A	4-2	4-(aminomethyl)-6-(6-methylimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 306.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.52 (br s, 1H), 8.60 (s, 1H), 8.43 - 8.31 (m, 2H), 8.21 - 8.06 (m, 1H), 8.03 - 7.89 (m, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.26 (dd, J = 1.2, 9.2 Hz, 1H), 4.09 (s, 2H), 2.36 - 2.33 (s, 3H)
4-21		4A	4-1	4-(aminomethyl)-6-(6-fluoroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 310.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 - 13.01 (s, 1H), 9.20 - 9.16 (m, 1H), 8.45 (br d, J = 0.8 Hz, 3H), 8.43 (d, J = 8.4 Hz, 1H), 8.29 (m, 2H), 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 7.96 - 7.89 (m, 1H), 7.74 - 7.64 (m, 1H), 4.61 - 4.55 (m, 2H)

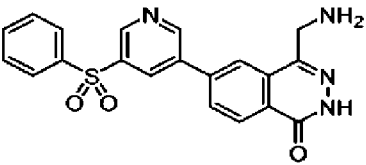
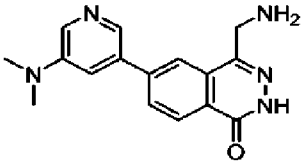
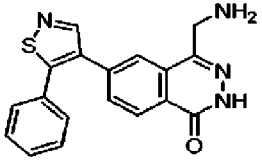
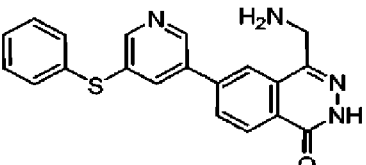
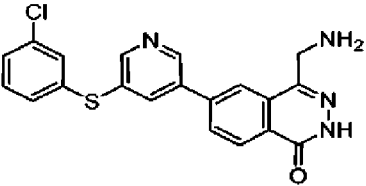
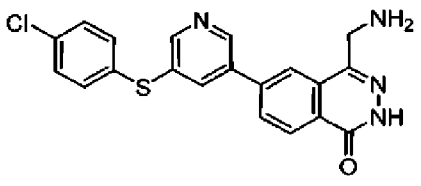
4-22		4A	4-1	4-(aminomethyl)-6-(8-fluoroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 310.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 8.81 (d, J = 6.8 Hz, 1H), 8.58 (br s, 3H), 8.44 (d, J = 8.4 Hz, 1H), 8.30 (s, 1H), 8.27 - 8.19 (m, 2H), 7.44 (dd, J = 7.6, 10.8 Hz, 1H), 7.11 (dt, J = 5.2, 7.2 Hz, 1H), 4.76 - 4.34 (m, 2H)
4-23		4A	4-1	4-(aminomethyl)-6-(2-methylimidazo[1,2-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 307.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (s, 1H), 9.41 - 9.25 (m, 1H), 8.90 - 8.79 (m, 1H), 8.71 (s, 3H), 8.48 (d, J = 8.4 Hz, 1H), 8.33 (br s, 1H), 8.14 (dd, J = 1.2, 8.2 Hz, 1H), 8.12 - 8.04 (m, 1H), 4.52 (br d, J = 5.6 Hz, 2H), 2.59 (s, 3H)
4-24		4A	4-1	4-(aminomethyl)-6-(6-methylimidazo[1,2-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 307.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.05 (s, 1H), 9.25 (d, J = 0.8 Hz, 1H), 8.89 (s, 1H), 8.61 (br s, 3H), 8.45 (d, J = 8.4 Hz, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 8.27 (dd, J = 1.2, 8.4 Hz, 1H), 4.65 - 4.52 (d, J = 5.6 Hz, 2H), 2.54 (s, 3H)
4-25		4A	4-2	4-(aminomethyl)-6-(imidazo[1,2-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 293.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.17 (d, J = 1.6 Hz, 1H), 8.71 (dd, J = 1.6, 4.8 Hz, 1H), 8.45 - 8.39 (m, 2H), 8.24 (s, 1H), 8.16 (dd, J = 1.6, 8.4 Hz, 1H), 8.00 (d, J = 4.8 Hz, 1H), 4.12 (s, 2H)
4-26		4A	4-1	4-(aminomethyl)-6-(imidazo[1,2-b]pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 293.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.98 (s, 1H), 8.87 (dd, J = 1.6, 4.4 Hz, 1H), 8.84 (s, 1H), 8.79 (dd, J = 1.6, 8.4 Hz, 1H), 8.64 (br d, J = 1.2 Hz, 4H), 8.47 - 8.39 (m, 2H), 7.57 (dd, J = 4.4, 9.2 Hz, 1H), 4.56 (br d, J = 5.6 Hz, 2H)
4-27		4A	4-1	4-(aminomethyl)-6-(6-chloro-8-fluoroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 344.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.03 (s, 1H), 8.93 (d, J = 1.6 Hz, 1H), 8.55 (br s, 3H), 8.43 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 1.2 Hz, 1H), 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 8.17 (s, 1H), 7.65 (dd, J = 1.6, 10.8 Hz, 1H), 4.63 - 4.42 (d, J = 5.6 Hz, 2H)

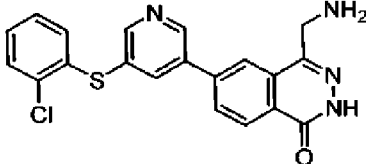
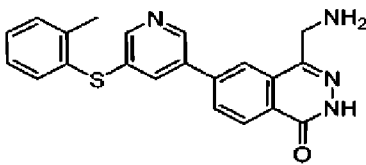
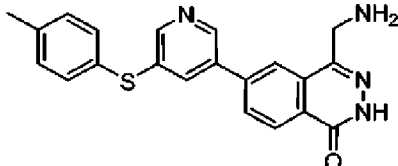
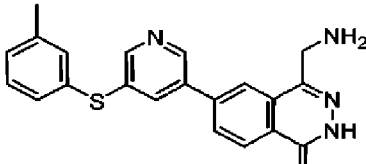
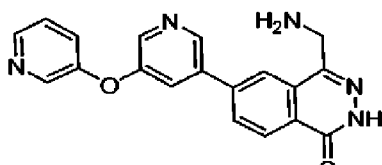
4-28		4A	4-1	4-(aminomethyl)-6-(7-chloroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 326.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 8.92 (d, J = 7.2 Hz, 1H), 8.43 - 8.41 (d, J = 8.4 Hz, 1H), 8.40 (s, 3H), 8.23 (s, 1H), 8.23 - 8.20 (dd, J = 1.2, 8.4 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 2.0, 7.2 Hz, 1H), 4.58 (br d, J = 2.0 Hz, 2H)
4-29		4A	4-1	4-(aminomethyl)-6-(7-fluoroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 310.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.80 (br s, 1H), 8.92 (br t, J = 6.4 Hz, 1H), 8.53 (m, 1H), 8.50 - 8.43 (brs, 3H), 8.25 (s, 1H), 8.22 - 8.17 (m, 1H), 8.15 (s, 1H), 7.65 - 7.60 (m, 1H), 7.15 (br t, J = 7.3 Hz, 1H), 4.53 (br s, 2H)
4-30		4A	4-1	4-(aminomethyl)-6-(7-methylimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 306.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.59 - 12.48 (s, 1H), 8.71 (d, J = 7.2 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 1.2 Hz, 1H), 8.11 (dd, J = 1.6, 8.4 Hz, 1H), 7.97 (s, 1H), 7.50 (s, 1H), 6.90 (dd, J = 1.6, 7.2 Hz, 1H), 4.11 - 4.05 (s, 2H), 2.41 (s, 3H)
4-31		4A	4-1	4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazole-5-carbonitrile LCMS [M+1] ⁺ = 281.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 8.50 (br s, 3H), 8.45 (s, 1H), 8.43 - 8.40 (d, J = 8.8 Hz, 1H), 8.23 (s, 1H), 8.22 - 8.20 (dd, J = 1.6, 8.8 Hz, 1H), 4.51 (br d, J = 5.6 Hz, 2H), 4.12 (s, 3H)
4-32		4A	4-1	4-(aminomethyl)-6-(1-methyl-5-phenyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 332.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.82 (s, 1H), 8.45 (br s, 3H), 8.386 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.7 (s, 1H), 7.6 (m, 3H), 7.501 (s, 1H), 7.437 (m, 2H), 4.23 (bs, 2H), 3.74 (s, 3H)
4-33		4A	4-2	4-(aminomethyl)-6-(6-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 324.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.70 - 11.56 (s, 1H), 7.70 (dd, J = 2.0, 4.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H), 7.08 (dd, J = 1.6, 8.4 Hz, 1H), 6.73 (dd, J = 5.2, 9.8 Hz, 1H), 6.51 - 6.43 (m, 1H), 3.12 (s, 2H), 1.52 (s, 3H)

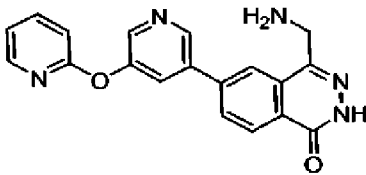
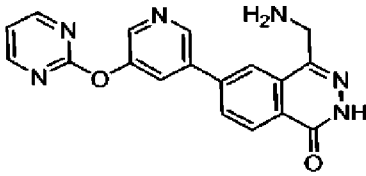
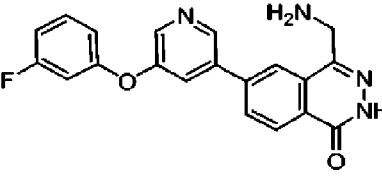
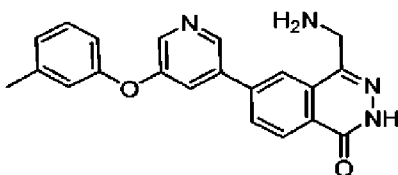
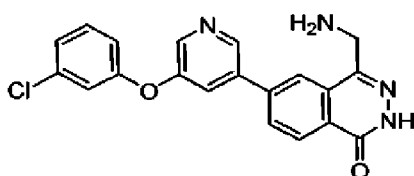
4-34		4A	4-4	4-(aminomethyl)-6-(6-chloroimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 326.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.04 (d, J = 1.2 Hz, 1H), 8.45 - 8.42 (m, 1H), 8.42 - 8.35 (s, 3H), 8.30 - 8.21 (m, 2H), 8.16 - 8.13 (m, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 2.0, 9.6 Hz, 1H), 4.59 (q, J = 5.2 Hz, 2H)
4-35		4B	4-1	3-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)imidazo[1,2-a]pyridine-7-carbonitrile LCMS [M+1] ⁺ = 317.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.05 (s, 1H), 9.13 (d, J = 6.8 Hz, 1H), 8.68 (br s, 3H), 8.59 (s, 1H), 8.49 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 1.2 Hz, 1H), 8.23 (dd, J = 1.2, 8.4 Hz, 1H), 7.45 (dd, J = 1.6, 7.2 Hz, 1H), 4.55 (br d, J = 5.6 Hz, 2H), 2.54 (s, 1H)
4-36		4A	4-2	4-(aminomethyl)-6-(6-ethoxyimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 336.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.99 (s, 1H), 7.67 (d, J = 9.6 Hz, 1H), 7.20 (dd, J = 2.4, 9.6 Hz, 1H), 4.42 (br s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H)
4-37		4A	4-5	4-(aminomethyl)-6-(6-cyclopropoxyimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 348.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.81 (s, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 1.2 Hz, 1H), 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (s, 1H), 7.68 (d, J = 9.6 Hz, 1H), 7.20 (dd, J = 2.0, 9.6 Hz, 1H), 6.87 - 6.32 (br s, 2H), 4.37 (d, J = 5.6 Hz, 1H), 4.00 (tt, J = 3.2, 5.6 Hz, 1H), 0.83 - 0.74 (m, 4H)
4-38		4A	4-1	4-(aminomethyl)-6-(6-(trifluoromethoxy)imidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 376.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.05 (s, 1H), 9.34 (s, 1H), 8.66 (br s, 3H), 8.52 (s, 1H), 8.49 - 8.43 (dd, J = 2.0, 8.4 Hz, 1H), 8.38 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 9.6 Hz, 1H), 7.89 (d, J = 9.6 Hz, 1H), 4.52 (br d, J = 5.2 Hz, 2H)
4-39		4A	4-5	4-(aminomethyl)-6-(6-phenylimidazo[1,2-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 368.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.05 (s, 1H), 9.01 (s, 1H), 8.61 - 8.38 (m, 5H), 8.36 - 8.29 (m, 2H), 8.02 (m, 2H), 7.84 - 7.77 (m, 2H), 7.57 - 7.49 (m, 2H), 7.48 - 7.42 (m, 1H), 4.62 - 4.55 (s, 2H)

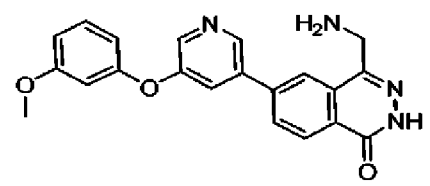
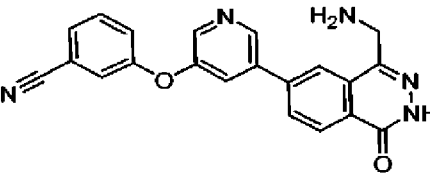
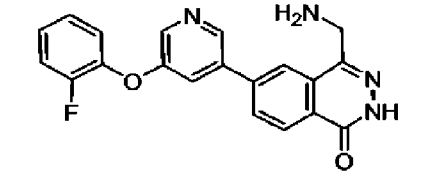
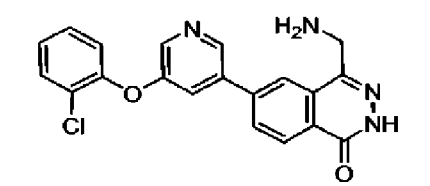
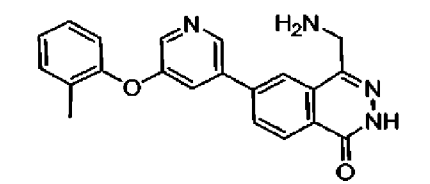
4-40		4A	4-1	4-(aminomethyl)-6-(3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 306.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.93 (s, 1H), 11.69 (br s, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.57 (br s, 4H), 8.39 – 8.37 (m, 1H), 8.36 – 8.34 (s, 1H), 8.29 (s, 1H), 7.37 (s, 1H), 4.65 – 4.59 (d, J = 5.6 Hz, 2H), 2.36 (s, 3H)
4-41		4A	4-1	5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile LCMS [M+1] ⁺ = 317.1 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.12 – 13.06 (s, 1H), 12.97 (s, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.8 Hz, 1H), 8.49 (br s, 3H), 8.39 (m, 2H), 8.34 (s, 1H), 4.71 – 4.59 (d, J = 5.6 Hz, 2H)
4-42		4A	4-4	4-(aminomethyl)-6-(3-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 310.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.95 (s, 1H), 11.75 – 11.72 (s, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.39 (br s, 3H), 8.37 (m, 1H), 8.36 (m, 1H), 8.29 (s, 1H), 7.59 (t, J = 2.4 Hz, 1H), 4.63 (br d, J = 5.6 Hz, 2H)
4-43		4A	4-1	4-(aminomethyl)-6-(3-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 360.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.97 (s, 1H), 12.77 (s, 1H), 8.94 (d, J = 2.0 Hz, 1H), 8.52 (s, 1H), 8.47 (s, 3H), 8.40 – 8.36 (m, 1H), 8.36 – 8.31 (m, 1H), 8.28 (m, 2H), 4.65 (d, J = 5.6 Hz, 2H)
4-44		4A	4-2	4-(aminomethyl)-6-(3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 326.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.95 (s, 1H), 12.23 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.46 – 8.38 (s, 3H), 8.38 – 8.34 (m, 2H), 8.30 (s, 1H), 7.81 (d, J = 2.8 Hz, 1H), 4.65 (br d, J = 4.0 Hz, 2H).
4-45		4A	4-5	4-(aminomethyl)-6-(3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 320.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.95 – 12.88 (s, 1H), 11.59 – 11.49 (s, 1H), 8.76 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.43 – 8.36 (br s, 3H), 8.35 – 8.30 (m, 2H), 8.23 (s, 1H), 7.33 (s, 1H), 4.71 – 4.57 (m, 2H), 2.79 (q, J = 7.2 Hz, 2H), 1.34 – 1.27 (q, J = 7.6 Hz, 3H)

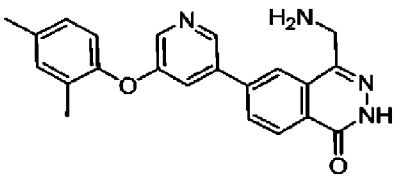
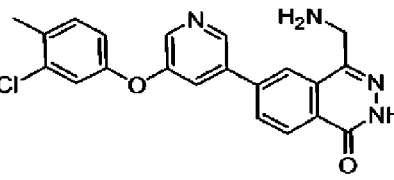
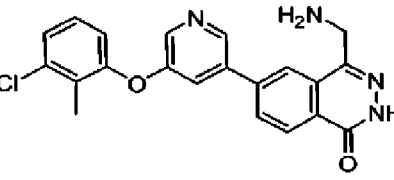
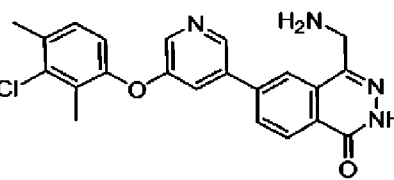
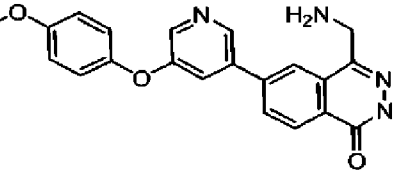
4-46		4A	4-2	4-(aminomethyl)-6-(3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 366.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.75 - 12.60 (s, 1H), 11.86 - 11.78 (s, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.38 - 8.34 (m, 1H), 8.31 (d, J = 1.2 Hz, 1H), 8.27 - 8.23 (m, 1H), 7.59 (d, J = 2.0 Hz, 1H), 4.65 (s, 2H), 4.34 (s, 2H), 3.28 (s, 3H)
4-47		4A	4-5	4-(aminomethyl)-6-(3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 322.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.68 (d, J = 2.0 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.17 (dd, J = 1.6, 8.4 Hz, 1H), 7.41 (s, 1H), 4.75 (s, 2H), 4.14 (s, 2H)
4-48		4A	4-2	4-(aminomethyl)-6-(5-methoxy-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 286.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.41 (br s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 1.2 Hz, 1H), 8.03 (dd, J = 1.6, 8.4 Hz, 1H), 8.00 (s, 1H), 4.09 - 3.97 (s, 2H), 3.90 (s, 3H), 3.73 (s, 3H).
4-49		4A	4-1	4-(aminomethyl)-6-(5-chloro-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 290.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.92 (s, 1H), 8.53 (br s, 3H), 8.34 (d, J = 8.4 Hz, 1H), 8.26 (s, 1H), 8.20 (dd, J = 1.6, 8.4 Hz, 1H), 8.10 (d, J = 1.2 Hz, 1H), 4.52 (br d, J = 5.6 Hz, 2H), 3.91 (s, 3H)
4-50		4A	4-1	4-(aminomethyl)-6-(5-benzylpyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 343.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.67 (d, J = 1.6 Hz, 1H), 8.48 (br s, 3H), 8.41 - 8.37 (m, 1H), 8.35 (t, J = 2.0 Hz, 1H), 8.29 - 8.20 (m, 2H), 7.37 - 7.27 (m, 4H), 7.23 - 7.18 (m, 1H), 4.60 (br d, J = 5.6 Hz, 2H), 4.12 (s, 2H)
4-51		4A	4-5	4-(aminomethyl)-6-(5-(hydroxy(phenyl)methyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 359.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.7 (br s, 1H), 8.96 (d, J = 2.4 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 1.2 Hz, 1H), 8.24 (s, 1H), 8.17 (dd, J = 1.6, 8.4 Hz, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.38 - 7.30 (m, 2H), 7.27 - 7.16 (m, 1H), 6.22 (br d, J = 3.6 Hz, 1H), 5.91 (br s, 1H), 4.27 (br s, 2H)

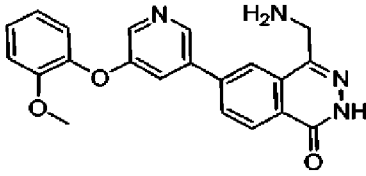
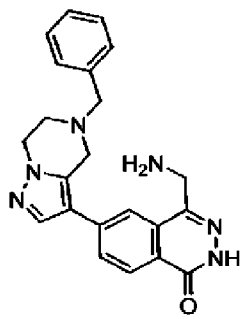
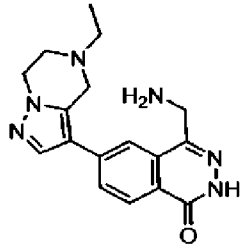
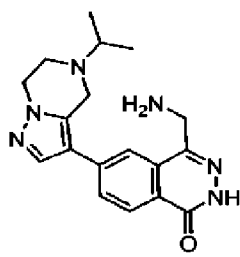
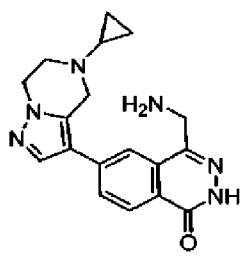
4-52		4A	4-6	4-(aminomethyl)-6-(5-(phenylsulfonyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 393.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.02 (s, 1H), 9.43 (d, J = 1.2 Hz, 1H), 9.24 (d, J = 1.2 Hz, 1H), 8.87 (s, 1H), 8.63 (br s, 3H), 8.42 - 8.32 (m, 3H), 8.15 (br d, J = 7.6 Hz, 2H), 7.74 (br d, J = 7.2 Hz, 1H), 7.70 - 7.64 (m, 2H), 4.60 (br d, J = 5.2 Hz, 2H).
4-53		4A	4-1	4-(aminomethyl)-6-(5-(dimethylamino)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 296.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.06 (s, 1H), 8.70 (s, 1H), 8.68 (s, 3H), 8.46 - 8.35 (m, 3H), 8.26 (d, J = 2.4 Hz, 1H), 8.09 (s, 1H), 4.60 (br d, J = 5.6 Hz, 2H), 3.17 (s, 6H).
4-54		4A	4-6	4-(aminomethyl)-6-(5-phenylisothiazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 335.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.96 (s, 1H), 8.96 (s, 1H), 8.45 (br s, 3H), 8.18 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 1.2 Hz, 1H), 7.65 (dd, J = 1.6, 8.2 Hz, 1H), 7.49 - 7.41 (m, 3H), 7.37 (m, 1H), 7.35 (m, 1H), 4.38 (s, 2H).
4-55		4A	4-1	4-(aminomethyl)-6-(5-(phenylthio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 361.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.12 (d, J = 2.0 Hz, 1H), 8.61 (br s, 3H), 8.55 (d, J = 2.0 Hz, 1H), 8.46 (t, J = 2.0 Hz, 1H), 8.39 - 8.35 (m, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.30 - 8.26 (m, 1H), 7.49 - 7.36 (m, 5H), 4.58 (br d, J = 5.6 Hz, 2H).
4-56		4A	4-4	4-(aminomethyl)-6-(5-((3-chlorophenyl)thio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 395.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 2.4 Hz, 1H), 8.50 (t, J = 2.0 Hz, 1H), 8.49 - 8.41 (m, 3H), 8.40 - 8.37 (m, 1H), 8.33 - 8.30 (m, 2H), 7.45 - 7.43 (m, 1H), 7.43 - 7.36 (m, 2H), 7.36 - 7.32 (m, 1H), 4.60 (br d, J = 5.6 Hz, 2H).
4-57		4A	4-4	4-(aminomethyl)-6-(5-((4-chlorophenyl)thio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 395.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 9.11 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.44 (t, J = 2.0 Hz, 1H), 8.43 - 8.33 (m, 4H), 8.31 - 8.28 (m, 2H), 7.50 - 7.46 (m, 2H), 7.45 - 7.42 (m, 2H), 4.60 (d, J = 5.2 Hz, 2H).

4-58		4A	4-5	4-(aminomethyl)-6-(5-((2-chlorophenyl)thio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 395.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.06 - 12.98 (s, 1H), 9.19 (d, J = 2.4 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.52 (t, J = 2.0 Hz, 1H), 8.49 - 8.38 (s, 3H), 8.38 - 8.35 (m, 1H), 8.34 - 8.30 (m, 2H), 7.65 - 7.57 (m, 1H), 7.40 - 7.30 (m, 2H), 7.20 - 7.12 (m, 1H), 4.61 (d, J = 5.2 Hz, 2H)
4-59		4A	4-4	4-(aminomethyl)-6-(5-(o-tolylthio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.03 (d, J = 2.0 Hz, 1H), 8.51 - 8.38 (m, 3H), 8.38 - 8.31 (m, 2H), 8.27 (br s, 1H), 8.27 - 8.26 (m, 1H), 8.24 (br d, J = 1.6 Hz, 1H), 7.42 - 7.37 (m, 1H), 7.36 - 7.31 (m, 2H), 7.29 - 7.24 (m, 1H), 4.59 (br d, J = 5.2 Hz, 2H), 2.40 (s, 3H)
4-60		4A	4-5	4-(aminomethyl)-6-(5-(p-tolylthio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.91 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.31 (s, 1H), 8.13 - 8.09 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.15 - 4.09 (m, 2H), 2.35 (s, 3H)
4-61		4A	4-2	4-(aminomethyl)-6-(5-(m-tolylthio)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.95 (s, 1H), 8.55 (d, J = 1.6 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.13 (br d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.21 (br d, J = 7.2 Hz, 1H), 4.19 - 4.05 (m, 2H), 2.33 (s, 3H)
4-62		4A	4-2	4-(aminomethyl)-6-(5-(pyridin-3-yloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 346.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.91 (d, J = 1.6 Hz, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.43 (dd, J = 1.2, 4.8 Hz, 1H), 8.38 - 8.33 (m, 2H), 8.16 (dd, J = 1.6, 8.4 Hz, 1H), 8.02 (t, J = 2.4 Hz, 1H), 7.59 (ddd, J = 1.2, 2.8, 8.4 Hz, 1H), 7.46 (dd, J = 4.4, 8.4 Hz, 1H), 4.12 (s, 2H)

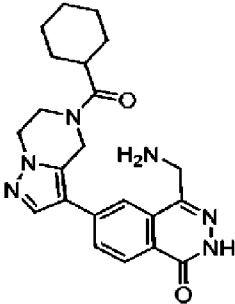
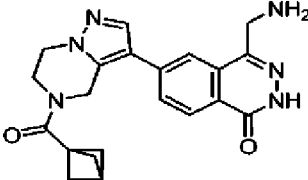
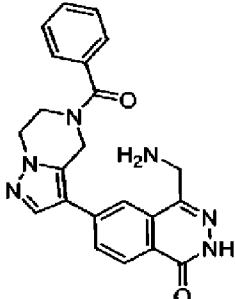
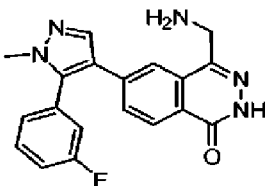
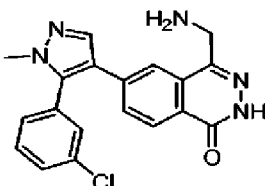
4-63		4A	4-5	4-(aminomethyl)-6-(5-(pyridin-2-yloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 346.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.03 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.38 (br d, J = 8.0 Hz, 4H), 8.35 - 8.29 (m, 2H), 8.26 (t, J = 2.0 Hz, 1H), 8.16 (dd, J = 1.2, 4.9 Hz, 1H), 7.94 (td, J = 2.0, 7.2, 8.4 Hz, 1H), 7.24 - 7.16 (m, 2H), 4.64 - 4.56 (d, J = 5.6 Hz, 2H).
4-64		4B	4-2	4-(aminomethyl)-6-(5-(pyrimidin-2-yloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 347.2; ¹ H NMR (400MHz, DMSO-d ₆) δ = 12.55 (br s, 1H), 9.02 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 4.8 Hz, 2H), 8.64 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.36 - 8.32 (m, 2H), 8.26 - 8.22 (m, 1H), 7.37 - 7.32 (m, 1H), 4.09 (s, 2H).
4-65		4A	4-1	4-(aminomethyl)-6-(5-(3-fluorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 363.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.09 (d, J = 2.0 Hz, 1H), 8.65 (br s, 3H), 8.55 (d, J = 2.8 Hz, 1H), 8.39 - 8.34 (m, 2H), 8.33 - 8.27 (m, 2H), 7.51 - 7.43 (m, 1H), 7.10 - 7.02 (m, 2H), 7.00 - 6.96 (d, J = 7.2 Hz, 1H), 4.61 - 4.54 (d, J = 6.0 Hz, 2H).
4-66		4A	4-1	4-(aminomethyl)-6-(5-(m-toloyloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 359.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.76 (s, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.54 - 8.31 (m, 5H), 8.31 - 8.26 (m, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.01 (t, J = 2.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.93 (dd, J = 2.8, 8.0 Hz, 1H), 4.55 (s, 2H), 2.34 (s, 3H)
4-67		4A	4-1	4-(aminomethyl)-6-(5-(3-chlorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 379.1; ¹ H NMR (400MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.03 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.44 (br s, 3H), 8.40 - 8.36 (d, J = 8.8 Hz, 1H), 8.33 - 8.28 (m, 2H), 8.18 (t, J = 2.4 Hz, 1H), 7.48 - 7.43 (t, J = 8.0 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.22 (t, J = 2.0 Hz, 1H), 7.10 (td, J = 0.8, 8.4 Hz, 1H), 4.60 (br d, J = 5.6 Hz, 2H)

4-68		4A	4-1	4-(aminomethyl)-6-(5-(3-methoxyphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.76 (s, 1H), 8.94 (d, J = 2.0 Hz, 1H), 8.48 (br s, 3H), 8.45 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H), 8.24 (dd, J = 1.6, 8.4 Hz, 1H), 8.04 (t, J = 2.4 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.80 (dd, J = 2.0, 8.0 Hz, 1H), 6.72 (t, J = 2.4 Hz, 1H), 6.71 - 6.67 (dd, J = 2.0, 6.8 Hz, 1H), 4.55 (s, 2H), 3.79 (s, 3H)
4-69		4A	4-1	3-((5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)oxy)benzonitrile LCMS [M+1] ⁺ = 370.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.12 (d, J = 2.0 Hz, 1H), 8.65 (br s, 3H), 8.60 (d, J = 2.8 Hz, 1H), 8.39 - 8.30 (m, 4H), 7.70 - 7.62 (m, 3H), 7.54 - 7.49 (m, 1H), 4.57 (br d, J = 5.6 Hz, 2H).
4-70		4A	4-5	4-(aminomethyl)-6-(5-(2-fluorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 363.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 (s, 1H), 8.97 (d, J = 1.6 Hz, 1H), 8.43 (br d, J = 2.4 Hz, 3H), 8.42 - 8.35 (m, 2H), 8.32 - 8.26 (m, 2H), 8.11 - 8.05 (m, 1H), 7.50 - 7.42 (m, 1H), 7.35 - 7.24 (m, 3H), 4.61 (br d, J = 5.6 Hz, 2H)
4-71		4A	4-1	4-(aminomethyl)-6-(5-(2-chlorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 379.1; ¹ H NMR (400MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 9.07 (d, J = 2.0 Hz, 1H), 8.67 (br s, 3H), 8.42 (d, J = 2.8 Hz, 1H), 8.39 - 8.35 (m, 2H), 8.31 - 8.27 (m, 1H), 8.25 (t, J = 2.0 Hz, 1H), 7.67 (dd, J = 1.2, 8.0 Hz, 1H), 7.42 (dd, J = 1.6, 7.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 4.58 (br d, J = 5.6 Hz, 2H).
4-72		4A	4-1	4-(aminomethyl)-6-(5-(o-tolyl)oxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 359.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 8.96 (d, J = 2.0 Hz, 1H), 8.54 (br s, 3H), 8.37 (d, J = 8.4 Hz, 1H), 8.33 - 8.30 (m, 2H), 8.26 (dd, J = 1.6, 8.4 Hz, 1H), 8.05 (t, J = 2.4 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.31 - 7.23 (td, J = 0.8, 7.2 Hz, 1H), 7.20 - 7.14 (td, J = 0.8, 7.2 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H), 2.27 (s, 3H)

4-73		4A	4-6	4-(aminomethyl)-6-(5-(2,4-dimethylphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 373.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 8.94 (d, J = 1.8 Hz, 1H), 8.56 (br s, 3H), 8.38 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 1.6, 8.4 Hz, 1H), 8.01 (t, J = 2.2 Hz, 1H), 7.20 (s, 1H), 7.08 (dd, J = 2.0, 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H), 2.31 (s, 3H), 2.21 (s, 3H)
4-74		4A	4-2	4-(aminomethyl)-6-(5-(3-chloro-4-methylphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 393.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.60 - 12.48 (s, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.20 (dd, J = 1.6, 8.4 Hz, 1H), 8.07 (t, J = 2.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 2.4, 8.4 Hz, 1H), 4.09 (s, 2H), 2.33 (s, 3H)
4-75		4A	4-2	4-(aminomethyl)-6-(5-(3-chloro-2-methylphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 393.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.55 (br s, 1H), 8.91 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 2.4 Hz, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.18 (dd, J = 1.6, 8.4 Hz, 1H), 7.99 (t, J = 2.4 Hz, 1H), 7.36 - 7.32 (dd, J = 1.6, 8.4 Hz, 1H), 7.31 - 7.25 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 4.09 (s, 2H), 2.34 (s, 3H)
4-76		4A	4-2	4-(aminomethyl)-6-(5-(3-chloro-2,4-dimethylphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 407.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.54 (br s, 1H), 8.85 (d, J = 1.6 Hz, 1H), 8.34 (s, 1H), 8.31 (m, 2H), 8.14 (br d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.25 (br d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.08 (s, 2H), 2.33 (s, 3H), 2.30 (s, 3H)
4-77		4A	4-1	4-(aminomethyl)-6-(5-(4-methoxyphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 8.95 (d, J = 2.0 Hz, 1H), 8.55 (br s, 3H), 8.39 - 8.36 (m, 2H), 8.31 (d, J = 1.2 Hz, 1H), 8.26 (dd, J = 1.6, 8.4 Hz, 1H), 8.05 (t, J = 2.2 Hz, 1H), 7.17 - 7.14 (m, 2H), 7.04 - 7.00 (m, 2H), 4.58 (br d, J = 5.6 Hz, 2H), 3.77 (s, 3H)

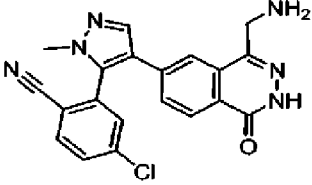
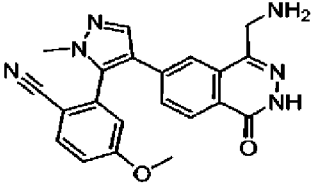
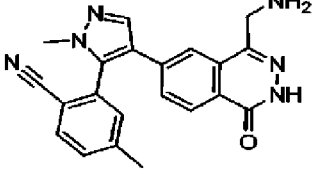
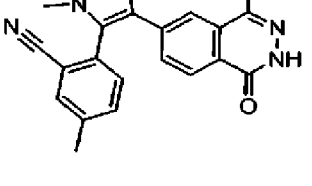
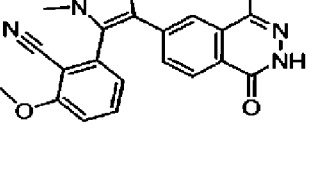
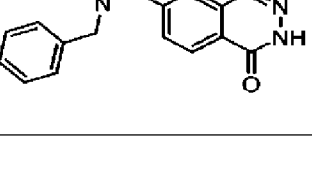
4-78		4A	4-1	4-(aminomethyl)-6-(5-(2-methoxyphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 375.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.99 (s, 1H), 8.89 (d, J = 1.6 Hz, 1H), 8.53 (br s, 3H), 8.37 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 1.2 Hz, 1H), 8.25 - 8.21 (m, 2H), 7.96 - 7.93 (t, J = 2.0 Hz, 1H), 7.32 - 7.27 (dt, J = 1.6, 7.6 Hz, 1H), 7.26 - 7.22 (dd, J = 1.6, 8.4 Hz, 1H), 7.21 (dd, J = 1.6, 7.6 Hz, 1H), 7.04 (dt, J = 1.6, 7.6 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H), 3.78 (s, 3H)
4-79		4B	4-2	4-(aminomethyl)-6-(5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 387.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.40 (br s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 7.88 (s, 1H), 7.85 (dd, J = 1.6, 8.4 Hz, 1H), 7.42 - 7.31 (m, 4H), 7.30 - 7.23 (m, 1H), 4.18 (br t, J = 5.4 Hz, 2H), 3.99 (s, 2H), 3.95 (s, 2H), 3.81 (s, 2H), 2.98 (br t, J = 5.4 Hz, 2H)
4-80		4B	4-4	4-(aminomethyl)-6-(5-ethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 325.3; ¹ H NMR (400 MHz, MeOD) δ = 8.44 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.97 (dd, J = 1.6, 8.4 Hz, 1H), 7.90 (s, 1H), 5.02 (s, 2H), 4.71 (s, 2H), 4.64 (br t, J = 5.6 Hz, 2H), 4.01 (br s, 2H), 3.58 (q, J = 7.2 Hz, 2H), 1.51 (t, J = 7.2 Hz, 3H)
4-81		4C	4-2	4-(aminomethyl)-6-(5-isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 339.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.25 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 7.95 (s, 1H), 7.87 (dd, J = 1.6, 8.4 Hz, 1H), 4.16 (t, J = 5.6 Hz, 2H), 4.08 (s, 2H), 4.02 (s, 2H), 3.03 (t, J = 5.6 Hz, 2H), 2.55 (td, J = 2.0, 4.0 Hz, 1H), 1.13 (d, J = 6.8 Hz, 6H)
4-82		4B	4-2	4-(aminomethyl)-6-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 337.3; ¹ H NMR (400 MHz, MeOD) δ = 8.36 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.87 (m, 2H), 4.23 (br s, 2H), 4.19 (s, 2H), 4.14 (s, 2H), 3.24 (br s, 2H), 2.07 (br s, 1H), 0.62 (br d, J = 5.2 Hz, 2H), 0.54 (br s, 2H)

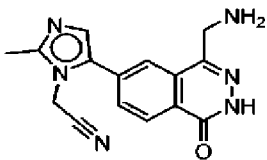
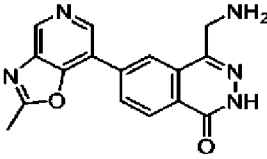
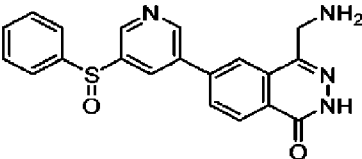
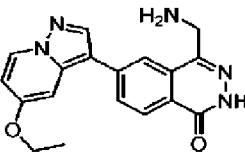
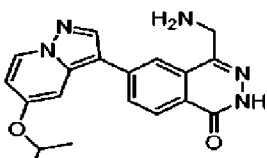
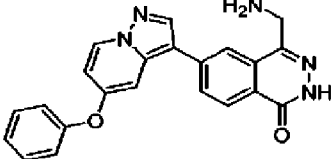
4-83		4A	4-1	4-(aminomethyl)-6-(5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 373.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.56 (br s, 3H), 8.31 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.05 (dd, J = 1.2, 8.4 Hz, 1H), 7.93 (d, J = 1.2, 1H), 7.31 - 7.23 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 4.82 (s, 2H), 4.58 (br d, J = 5.6 Hz, 2H), 4.29 (br t, J = 5.2 Hz, 2H), 3.85 (br t, J = 5.2 Hz, 2H)
4-84		4B	4-1	6-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)-4-(aminomethyl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 339.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.64 (br s, 1H), 8.55 (br s, 3H), 8.33 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.94 (br d, J = 8.4 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 5.05 (br s, 2H), 4.48 (br s, 2H), 4.26 (br s, 2H), 4.01 (t, J = 5.6 Hz, 2H), 2.18 (s, 3H)
4-85		4A	4-5	4-(aminomethyl)-6-(5-(cyclopropanecarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 365.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.41 (br s, 3H), 8.33 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.96 (dd, J = 1.2, 8.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 5.14 (s, 2H), 4.51 (s, 2H), 4.33 - 4.24 (m, 2H), 4.17 (br s, 2H), 2.18 - 2.11 (m, 1H), 0.84 - 0.79 (m, 4H).
4-86		4A	4-5	4-(aminomethyl)-6-(5-(cyclobutanecarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 379.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.2 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.89 (dd, J = 1.6, 8.4 Hz, 1H), 4.97 (s, 2H), 4.21 (t, J = 5.6 Hz, 2H), 4.09 (s, 2H), 3.95 (br s, 2H), 3.53 (t, J = 8.4 Hz, 1H), 2.30 - 2.18 (m, 4H), 2.00 - 1.89 (m, 1H), 1.87 - 1.75 (m, 1H)
4-87		4A	4-6	4-(aminomethyl)-6-(5-(cyclopentanecarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 393.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.64 (br s, 1H), 8.53 (br s, 3H), 8.33 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.94 (br d, J = 9.2 Hz, 1H), 7.91 (s, 1H), 5.07 (br s, 2H), 4.48 (s, 2H), 4.24 (br t, J = 5.2 Hz, 2H), 4.07 (br t, J = 5.2 Hz, 2H), 3.23 - 3.16 (m, 1H), 1.82 (m, 2H), 1.77 - 1.68 (m, 2H), 1.63 - 1.62 (m, 2H), 1.60 - 1.51 (m, 2H)

4-88		4A	4-4	4-(aminomethyl)-6-(5-(cyclohexanecarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+] ⁺ = 407.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.65 (br s, 1H), 8.52 (br s, 3H), 8.34 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 5.06 (s, 2H), 4.49 (br s, 2H), 4.28 - 4.22 (m, 2H), 4.09 - 4.04 (m, 2H), 2.84 - 2.75 (m, 1H), 1.73 - 1.70 (m, 5H), 1.45 - 1.23 (m, 5H)
4-89		4A	4-5	4-(aminomethyl)-6-(5-(bicyclo[1.1.1]pentane-1-carbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+] ⁺ = 391.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.45 (br s, 3H), 8.32 (br d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 8.00 - 7.88 (m, 2H), 5.24 - 4.95 (m, 2H), 4.52 (br s, 2H), 4.32 - 4.09 (m, 4H), 2.22 - 2.06 (m, 7H).
4-90		4A	4-5	4-(aminomethyl)-6-(5-(benzoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)phthalazin-1(2H)-one LCMS [M+] ⁺ = 401.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.90 (br s, 1H), 8.59 - 8.37 (s, 3H), 8.36 - 8.25 (m, 1H), 8.18 (s, 1H), 8.04 - 7.79 (m, 2H), 7.52 (br d, J = 4.0 Hz, 5H), 5.15 (br s, 2H), 4.52 (br s, 2H), 4.29 (br d, J = 4.8 Hz, 2H), 4.08 - 3.70 (m, 2H)
4-91		4A	4-5	4-(aminomethyl)-6-(5-(3-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+] ⁺ = 350.0 ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.40 (br s, 3H), 8.14 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 1.2 Hz, 1H), 7.64 - 7.54 (m, 1H), 7.51 (dd, J = 1.6, 8.4 Hz, 1H), 7.44 - 7.32 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 4.27 (s, 2H), 3.76 (s, 3H)
4-92		4A	4-5	4-(aminomethyl)-6-(5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+] ⁺ = 366.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.46 (br s, 3H), 8.16 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.60 - 7.55 (m, 2H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.40 (td, J = 1.2, 7.6 Hz, 1H), 4.32 - 4.27 (d, J = 5.6 Hz, 2H), 3.76 (s, 3H)

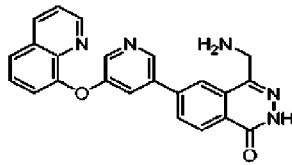
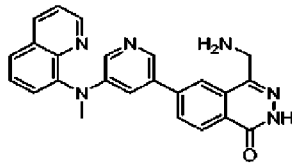
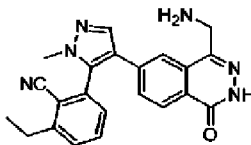
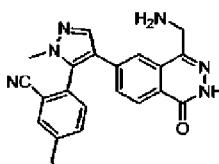
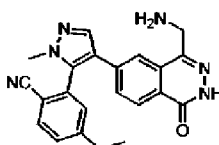
4-93		4A	4-4	4-(aminomethyl)-6-(5-(3-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 362.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.39 - 8.29 (s, 3H), 8.14 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.54 (dd, J = 1.6, 8.4 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.15 - 7.10 (dd, J = 2.8, 8.4 Hz, 1H), 7.01 - 6.99 (t, J = 1.2 Hz, 1H), 6.98 - 6.94 (dt, J = 7.6 Hz, 1H), 4.27 (br d, J = 4.8 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H).
4-94		4A	4-4	4-(aminomethyl)-6-(1-methyl-5-(m-tolyl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 346.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.35 (br s, 3H), 8.15 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.53 (dd, J = 1.2, 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 7.2 Hz, 1H), 4.24 (br s, 2H), 3.73 (s, 3H), 2.36 (s, 3H)
4-95		4A	4-1	4-(aminomethyl)-6-(5-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 350.1; ¹ H NMR (400MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.49 (br s, 3H), 8.16 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.53 - 7.46 (m, 3H), 7.43 - 7.37 (m, 2H), 4.28 (br d, J = 5.6 Hz, 2H), 3.74 (s, 3H)
4-96		4A	4-1	4-(aminomethyl)-6-(5-(4-chlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 366.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.54 (br s, 3H), 8.16 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.48 - 7.45 (dd, J = 1.2, 8.4 Hz, 2H), 7.43 (dd, J = 1.2, 8.4 Hz, 1H), 4.33 (br d, J = 5.6 Hz, 2H), 3.75 (s, 3H)
4-97		4A	4-4	4-(aminomethyl)-6-(1-methyl-5-(p-tolyl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 346.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.34 (br s, 3H), 8.13 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 1.2 Hz, 1H), 7.52 (dd, J = 1.6, 8.4 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.33 - 7.28 (m, 2H), 4.27 (br s, 2H), 3.73 (s, 3H), 2.42 (s, 3H)

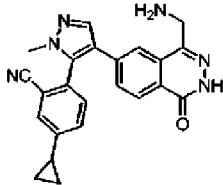
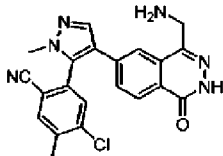
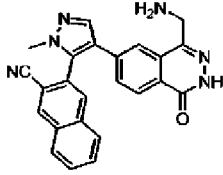
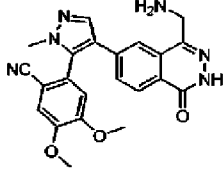
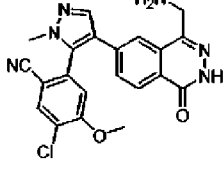
4-98		4A	4-5	4-(aminomethyl)-6-(5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 362.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.36 (br s, 3H), 8.12 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 1.2 Hz, 1H), 7.52 (dd, J = 1.6, 8.4 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.15 - 7.06 (m, 2H), 4.30 (br d, J = 4.0 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H).
4-99		4A	4-1	4-(aminomethyl)-6-(1-methyl-5-(6-methylpyridin-3-yl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 347.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.73 (s, 1H), 8.58 (br s, 3H), 8.22 (s, 1H), 8.17 (br d, J = 7.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.77 (br d, J = 8.4 Hz, 1H), 7.52 (dd, J = 1.2, 8.4 Hz, 1H), 4.31 (br d, J = 5.6 Hz, 2H), 3.81 (s, 3H), 2.73 (s, 3H)
4-100		4A	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzonitrile LCMS [M+1] ⁺ = 357.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.36 (br s, 3H), 8.28 (s, 1H), 8.09 (m, 2H), 7.99 - 7.89 (td, J = 1.2 Hz, 7.6 Hz, 1H), 7.80 (t, J = 7.6 Hz, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 4.24 (br d, J = 12.4 Hz, 2H), 3.74 (s, 3H).
4-101		4A	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-chlorobenzonitrile LCMS [M+1] ⁺ = 391.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.59 - 8.44 (br s, 3H), 8.31 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 2.4, 8.4 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 1.2, 8.4 Hz, 1H), 4.34 (d, J = 5.6 Hz, 2H), 3.74 (s, 3H)
4-102		4G	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-chloro-6-cyclopropoxybenzonitrile LCMS [M+1] ⁺ = 447.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.52 (br s, 3H), 8.39 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.42 (dd, J = 1.6, 8.4 Hz, 1H), 4.29 (br s, 2H), 4.24 - 4.17 (m, 1H), 3.69 (s, 3H), 0.90 (br dd, J = 3.4, 5.9 Hz, 2H), 0.87 - 0.74 (m, 2H)

4-103		4A	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chlorobenzonitrile LCMS [M+1] ⁺ = 391.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.50 (br s, 3H), 8.31 (s, 1H), 8.11 (m, 2H), 8.01 (d, J = 2.0 Hz, 1H), 7.91 (dd, J = 2.0, 8.6 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.42 (dd, J = 1.6, 8.4 Hz, 1H), 4.29 (d, J = 6.4 Hz, 2H), 3.77 (s, 3H)
4-104		4A	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-methoxybenzonitrile LCMS [M+1] ⁺ = 387.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.58 - 8.45 (s, 3H), 8.30 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.37 - 7.36 (m, 1H), 7.35 - 7.32 (m, 1H), 4.34 - 4.19 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H)
4-105		4A	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-methylbenzonitrile LCMS [M+1] ⁺ = 371.1; ¹ H NMR (400 MHz, MeOD) δ = 8.20 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.59 (s, 1H), 7.54 (dd, J = 1.6, 8.4 Hz, 1H), 4.45 - 4.29 (m, 2H), 3.81 (s, 3H), 2.54 (s, 3H)
4-106		4A	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-methylbenzonitrile LCMS [M+1] ⁺ = 371.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.44 (br s, 3H), 8.26 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.79 - 7.72 (m, 1H), 7.71 - 7.59 (m, 2H), 7.45 (br d, J = 8.4 Hz, 1H), 4.31 (d, J = 11.2 Hz, 2H), 3.72 (s, 3H), 2.47 (s, 3H)
4-107		4A	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-methoxybenzonitrile LCMS [M+1] ⁺ = 387.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.59 (br s, 3H), 8.31 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.89 (d, 8.4 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.28 (d, J = 7.6 Hz, 1H), 4.24 (br d, J = 5.6 Hz, 2H), 4.00 (s, 3H), 3.72 (s, 3H)
4-108		4B	4-7	4-(aminomethyl)-6-(1-benzyl-1H-imidazol-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 332.1; ¹ H NMR (400 MHz, MeOD) δ = 8.35 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.88 (dd, J = 1.6, 8.4 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.37 (d, J = 0.8 Hz, 1H), 7.34 - 7.24 (m, 3H), 7.02 (d, J = 6.8 Hz, 2H), 5.45 (s, 2H), 3.92 (s, 2H)

4-109		4A	4-3	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-2-methyl-1H-imidazol-1-yl)acetonitrile ¹ H NMR (400 MHz, MeOD) δ = 8.59 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.07 (dd, J = 1.6, 8.4 Hz, 1H), 7.75 (s, 1H), 5.45 (s, 2H), 4.65 (s, 2H), 2.83 (s, 3H)
4-110		4B	4-2	4-(aminomethyl)-6-(2-methyloxazolo[4,5-c]pyridin-7-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 308.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.59 (br s, 1H), 9.05 (br s, 1H), 9.01 (br s, 1H), 8.58 (br s, 1H), 8.41 (br s, 1H), 8.38 (br s, 1H), 4.10 (d, J = 5.6 Hz, 2H), 2.73 (s, 3H)
4-111		4A	4-6	4-(aminomethyl)-6-(5-(phenylsulfinyl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 377.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.0 (s, 1H), 9.27 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.72 - 8.66 (m, 1H), 8.65 - 8.45 (br s, 3H), 8.44 - 8.37 (m, 1H), 8.36 - 8.32 (m, 1H), 8.30 (dd, J = 1.6, 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.89 - 7.84 (m, 1H), 7.62 - 7.52 (m, 3H), 4.59 (br d, J = 5.6 Hz, 2H)
4-112		4B	4-4	4-(aminomethyl)-6-(5-ethoxypyrazolo[1,5-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 336.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.68 (d, J = 7.6 Hz, 1H), 8.62 (m, 4H), 8.32 - 8.29 (m, 1H), 8.25 - 8.21 (m, 1H), 8.09 (s, 1H), 7.41 (d, J = 2.4 Hz, 1H), 6.73 (dd, J = 2.4, 7.6 Hz, 1H), 4.58 (br d, J = 5.6 Hz, 2H), 4.24 (q, J = 6.8 Hz, 2H), 1.41 (t, J = 6.8 Hz, 3H)
4-113		4B	4-4	4-(aminomethyl)-6-(5-isopropoxypyrazolo[1,5-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 350.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.68 (d, J = 7.6 Hz, 1H), 8.60 (s, 4H), 8.33 - 8.28 (m, 1H), 8.21 (dd, J = 1.2, 8.4 Hz, 1H), 8.08 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 2.4, 7.6 Hz, 1H), 4.94 (td, J = 6.0, 12.0 Hz, 1H), 4.58 (br d, J = 5.2 Hz, 2H), 1.37 (s, 3H), 1.36 (s, 3H)
4-114		4B	4-4	4-(aminomethyl)-6-(5-phenoxy pyrazolo[1,5-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 384.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.84 (d, J = 7.6 Hz, 1H), 8.66 (s, 1H), 8.43 (br s, 3H), 8.28 (d, J = 8.4 Hz, 1H), 8.16 (br d, J = 7.6 Hz, 1H), 8.01 (d, J = 1.2 Hz, 1H), 7.63 (br s, 1H), 7.53 - 7.46 (m, 2H), 7.29 - 7.25 (m, 1H), 7.24 - 7.21 (m, 2H), 6.81 (dd, J = 2.4, 7.6 Hz, 1H), 4.53 (br s, 2H)

4-115		4B	4-4	4-(aminomethyl)-6-(5-(benzyloxy)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 362.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.41 (br s, 3H), 8.27 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.43 - 7.36 (m, 5H), 5.07 (s, 2H), 4.45 (br s, 2H), 3.61 (s, 3H)
4-116		4A	4-2	4-(aminomethyl)-6-(5-(cyclopropylmethoxy)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 326.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.78 (br s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.14 (dd, J = 1.6, 8.4 Hz, 1H), 8.06 (s, 1H), 8.03 (d, J = 1.2 Hz, 1H), 8.00 - 7.43 (br s, 2H), 4.43 (s, 2H), 3.90 (d, J = 7.6 Hz, 2H), 3.75 (s, 3H), 1.26 - 1.21 (m, 1H), 0.53 (m, 2H), 0.27 - 0.20 (m, 2H)
4-117		4B	4-4	4-(aminomethyl)-6-(1-methyl-5-phenethyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 360.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.63 (br s, 3H), 8.26 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.87 (dd, J = 1.2, 8.4 Hz, 1H), 7.82 (s, 1H), 7.23 (d, J = 7.6 Hz, 2H), 7.19 - 7.13 (m, 3H), 4.50 (br d, J = 5.6 Hz, 2H), 3.76 (s, 3H), 3.19 (br t, J = 7.6 Hz, 2H), 2.86 (br t, J = 7.6 Hz, 2H)
4-118		4A	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-methylbenzonitrile LCMS [M+1] ⁺ = 371.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.43 - 8.29 (br s, 3H), 8.27 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.72 - 7.66 (m, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.46 (dd, J = 1.6, 8.4 Hz, 1H), 4.24 (br s, 2H), 3.70 (s, 3H), 2.55 (s, 3H)
4-119		4A	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chlorobenzonitrile LCMS [M+1] ⁺ = 298.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 7.98 (dd, J = 1.2, 6.8 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.77 (s, 1H), 7.69 (dd, J = 1.2 Hz, 1H), 3.75 (s, 3H)
4-120		4B	4-2	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)pyridine 1-oxide LCMS [M+1] ⁺ = 349.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.72 (br s, 1H), 8.54 (d, J = 6.4 Hz, 1H), 8.19 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.69 - 7.61 (m, 1H), 7.59 - 7.52 (m, 2H), 7.48 - 7.41 (td, J = 0.8, 7.6 Hz, 1H), 6.97 (br s, 2H), 4.14 (br d, J = 4.8 Hz, 2H), 3.74 (s, 3H)

4-121		4B	4-4	4-(aminomethyl)-6-(5-(quinolin-8-yloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 396.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.98 (s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.87 (dd, J = 1.6, 4.4 Hz, 1H), 8.49 (dd, J = 1.2, 8.4 Hz, 1H), 8.43 - 8.33 (m, 4H), 8.28 (d, J = 2.8 Hz, 2H), 8.24 (d, J = 8.4 Hz, 1H), 8.05 - 8.01 (t, J = 2.0 Hz, 1H), 7.94 - 7.90 (dd, J = 1.2, 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.62 (dd, J = 4.0, 8.4 Hz, 1H), 7.55 (dd, J = 1.2, 7.6 Hz, 1H), 4.61 - 4.57 (m, 2H)
4-122		4B	4-4	4-(aminomethyl)-6-(5-(methyl(quinolin-8-yl)amino)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 409.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 (s, 1H), 8.90 (dd, J = 1.6, 4.4 Hz, 1H), 8.76 (s, 1H), 8.73 - 8.60 (m, 4H), 8.41 - 8.37 (m, 2H), 8.29 - 8.25 (m, 1H), 8.17 (dd, J = 0.8, 8.4 Hz, 1H), 8.11 (s, 1H), 7.98 (dd, J = 1.2, 7.2 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 4.4, 8.4 Hz, 1H), 4.57 (br d, J = 5.6 Hz, 2H), 3.65 (s, 3H)
4-123		4B	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethylbenzonitrile LCMS [M+1] ⁺ = 385.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.54 (br s, 3H), 8.32 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.48 - 7.42 (m, 1H), 4.20 (br d, J = 11.6 Hz, 2H), 3.72 (s, 3H), 2.86 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H)
4-124		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-ethylbenzonitrile LCMS [M+1] ⁺ = 385.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.36 (m, 3H), 8.25 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.78 (dd, J = 1.6, 8.0 Hz, 1H), 7.70 (br s, 1H), 7.69 - 7.66 (m, 1H), 7.43 (br d, J = 8.4 Hz, 1H), 4.36 (d, J = 14.4 Hz, 2H), 3.73 (s, 3H), 2.78 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H)
4-125		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-ethylbenzonitrile LCMS [M+1] ⁺ = 385.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.50 - 8.29 (m, 3H), 8.27 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.71 - 7.63 (m, 2H), 7.63 (s, 1H), 7.47 (br d, J = 8.4 Hz, 1H), 4.35 - 4.10 (d, J = 9.6 Hz, 2H), 3.73 (s, 3H), 2.78 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H)

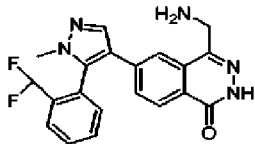
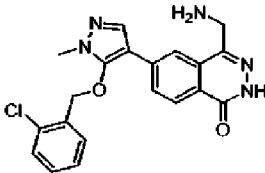
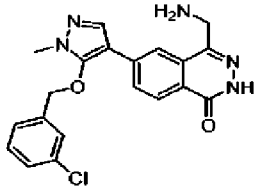
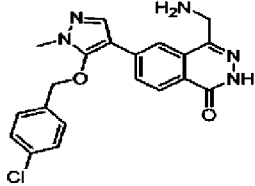
4-126		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-cyclopropylbenzonitrile LCMS [M+1] ⁺ = 397.2; ¹ H NMR (400 MHz, MeOD) δ = 8.20 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.74 (s, 1H), 7.64 (d, J = 1.2 Hz, 1H), 7.62 - 7.56 (m, 2H), 7.50 (br d, J = 8.4 Hz, 1H), 4.49 - 4.29 (m, 2H), 3.79 (s, 3H), 2.10 (s, 1H), 1.23 - 1.09 (m, 2H), 0.95 - 0.79 (m, 2H)
4-127		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-5-methylbenzonitrile LCMS [M+1] ⁺ = 405.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.36 (br s, 3H), 8.26 (s, 1H), 8.15 - 8.07 (m, 2H), 7.97 (s, 1H), 7.78 (s, 1H), 7.42 (dd, J = 1.6, 8.4 Hz, 1H), 4.34 (d, J = 10.8 Hz, 1H), 3.75 (s, 3H), 2.48 (s, 3H)
4-128		4B	4-4	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-naphthonitrile LCMS [M+1] ⁺ = 407.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.82 (s, 1H), 8.37 (s, 1H), 8.32 (s, 4H), 8.22 - 8.18 (m, 1H), 8.15 - 8.11 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.87 - 7.79 (m, 2H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 4.31 (br d, J = 0.8 Hz, 2H), 3.77 (s, 3H)
4-129		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4,5-dimethoxybenzonitrile LCMS [M+1] ⁺ = 417.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.37 (br s, 3H), 8.26 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.57 (s, 1H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.35 (s, 1H), 4.40 - 4.26 (br d, J = 5.6 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H)
4-130		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-chloro-4-methoxybenzonitrile LCMS [M+1] ⁺ = 421.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.37 (br s, 3H), 8.28 (s, 1H), 8.22 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 4.45 - 4.29 (m, 2H), 4.01 (s, 3H), 3.77 (s, 3H)

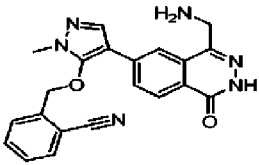
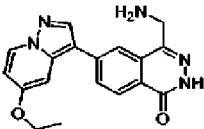
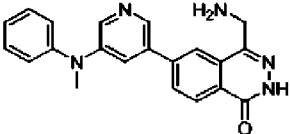
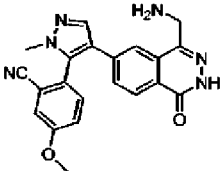
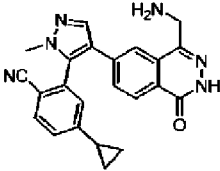
4-131		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4,5-dimethylbenzonitrile LCMS [M+1] ⁺ = 385.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.34 (br s, 3H), 8.27 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.58 (s, 1H), 7.44 (dd, J = 1.6, 8.4 Hz, 1H), 4.32 (d, J = 22.0 Hz, 2H), 3.71 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H)
4-132		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-chloro-4-methylbenzonitrile LCMS [M+1] ⁺ = 405.2; ¹ H NMR (400 MHz, MeOD) δ = 8.22 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.77 (s, 1H), 7.71 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.45 (d, J = 9.2 Hz, 2H), 3.81 (s, 3H), 2.55 (s, 3H)
4-133		4B	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-5-methoxybenzonitrile LCMS [M+1] ⁺ = 421.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.43 (br s, 3H), 8.27 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.84-7.82 (d, J = 1.6 Hz, 1H), 7.41 (dd, J = 1.6, 8.4 Hz, 1H), 4.40-4.30 (m, 2H), 4.01 (s, 3H), 3.74 (s, 3H)
4-134		4B	4-4	4-(aminomethyl)-6-(5-(4-ethylphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 360.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.51 - 8.28 (br s, 3H), 8.12 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.52 (dd, J = 1.2, 8.4 Hz, 1H), 7.42 - 7.37 (m, 2H), 7.36 - 7.30 (m, 2H), 4.26 (d, J = 5.6 Hz, 2H), 3.74 (s, 3H), 2.72 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H)
4-135		4B	4-5	4-(aminomethyl)-6-(5-(4-isopropylphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 374.2; ¹ H NMR (400 MHz, MeOD) δ = 8.13 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 7.66 - 7.60 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.27 (s, 2H), 3.77 (s, 3H), 3.07 - 2.98 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H)
4-136		4B	4-4	4-(aminomethyl)-6-(5-(4-cyclopropoxyphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 388.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.40 (br s, 3H), 8.11 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.53 (dd, J = 1.6, 8.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8

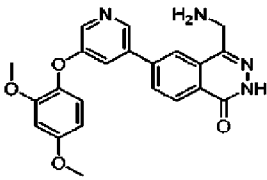
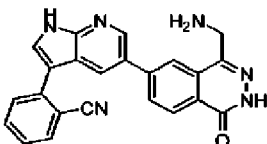
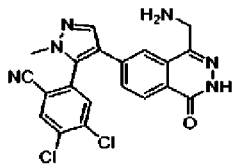
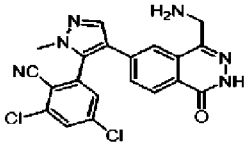
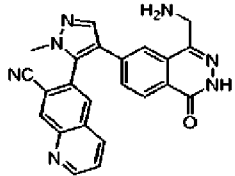
				Hz, 2H), 4.29 (br s, 2H), 3.93 (td, J = 3.2, 6.0 Hz, 1H), 3.73 (s, 3H), 0.88 - 0.79 (m, 2H), 0.75 - 0.67 (m, 2H)
4-137		4B	4-4	4-(aminomethyl)-6-(5-(3-cyclobutoxyphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 402.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.36 (br s, 3H), 8.13 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.52 (dd, J = 1.6, 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.02 (dd, J = 2.0, 8.4 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.85 - 6.82 (m, 1H), 4.69 (t, J = 7.2 Hz, 1H), 4.27 (s, 2H), 3.75 (s, 3H), 2.37 - 2.25 (m, 2H), 2.03 - 1.87 (m, 2H), 1.73 (q, J = 10.4 Hz, 1H), 1.64 - 1.50 (m, 1H)
4-138		4B	4-6	4-(aminomethyl)-6-(5-(4-cyclobutoxyphenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 402.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.82 (s, 1H), 8.60 - 8.36 (br s, 3H), 8.12 (s, 1H), 8.06 (dd, J = 1.2, 8.4 Hz, 1H), 7.79 (s, 1H), 7.52 - 7.46 (m, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.04 - 6.94 (m, 2H), 4.77 (quin, J = 7.2 Hz, 1H), 4.29 (br d, J = 5.6 Hz, 2H), 3.72 (s, 3H), 2.47 - 2.41 (m, 2H), 2.17 - 2.03 (m, 2H), 1.81 (q, J = 10.0 Hz, 1H), 1.72 - 1.60 (m, 1H)
4-139		4B	4-4	4-(aminomethyl)-6-(1-methyl-5-(naphthalen-2-yl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 382.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.82 (s, 1H), 8.35 (s, 3H), 8.19 (s, 1H), 8.10 - 7.95 (m, 5H), 7.89 (s, 1H), 7.68 - 7.57 (m, 2H), 7.48 (dd, J = 1.6, 8.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 4.31 (br s, 2H), 3.80 (s, 3H)
4-140		4B	4-4	4-(aminomethyl)-6-(5-(3,4-dichlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 400.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.36 (br s, 3H), 8.14 - 8.10 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 1.2 Hz, 1H), 7.79 (m, 2H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.40 (dd, J = 2.0, 8.4 Hz, 1H), 4.37 (s, 2H), 3.78 (s, 3H)
4-141		4B	4-4	4-(aminomethyl)-6-(5-(3,5-dichlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 400.0; ¹ H NMR (400 MHz, MeOD) δ = 8.26 (br d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.70 - 7.62 (m, 2H), 7.46 (d, J = 1.2 Hz, 2H), 4.39 (s, 2H), 3.83 (s, 3H)

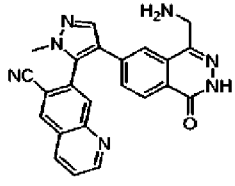
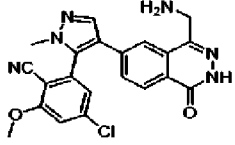
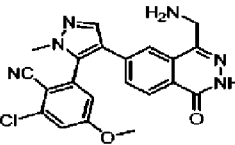
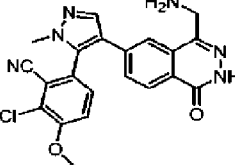
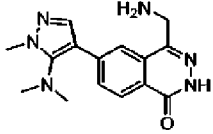
4-142		4B	4-4	4-(aminomethyl)-6-(5-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 350.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.40 - 8.28 (br s, 3H), 8.23 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.71 - 7.64 (m, 1H), 7.56 - 7.50 (m, 2H), 7.49 - 7.40 (m, 2H), 4.28 (br d, J = 5.6 Hz, 2H), 3.73 (s, 3H)
4-143		4B	4-4	4-(aminomethyl)-6-(5-(2-chlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 366.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.42 (br s, 3H), 8.26 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.76 - 7.72 (m, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.67 - 7.61 (m, 1H), 7.57 - 7.56 (m, 1H), 7.55 (d, J = 0.8 Hz, 1H), 7.49 (dd, J = 1.6, 8.4 Hz, 1H), 4.28 - 4.18 (m, 2H), 3.65 (s, 3H)
4-144		4B	4-5	4-(aminomethyl)-6-(5-(2,6-dichlorophenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 400.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.46 - 8.30 (m, 4H), 8.11 (d, J = 8.4 Hz, 1H), 7.79 - 7.75 (m, 2H), 7.74 (d, J = 1.2 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.43 (dd, J = 1.6, 8.4 Hz, 1H), 4.30 (br d, J = 5.2 Hz, 2H), 3.64 (s, 3H)
4-145		4B	4-5	5-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-ethoxybenzonitrile LCMS [M+1] ⁺ = 401.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.40 (br s, 3H), 8.13 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.64 (dd, J = 2.0, 8.8 Hz, 1H), 7.48 (dd, J = 1.2, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.34 (br s, 2H), 4.28 (q, J = 6.8 Hz, 2H), 3.75 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H)
4-146		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethoxybenzonitrile LCMS [M+1] ⁺ = 401.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.38 (br s, 3H), 8.27 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 7.6, 8.4 Hz, 1H), 7.76 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.26 (d, J = 7.6 Hz, 1H), 4.38 - 4.28 (m, 2H), 4.28 - 4.21 (m, 2H), 3.72 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H)

4-147		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS [M+1] ⁺ = 407.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.41 - 8.30 (m, 4H), 8.28 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.93 - 7.84 (m, 3H), 7.83 (d, J = 8.8 Hz, 1H), 7.33 (dd, J = 1.2, 8.4 Hz, 1H), 4.42 - 4.20 (m, 2H), 3.78 (s, 3H)
4-148		4B	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2,3-dichlorobenzonitrile LCMS [M+1] ⁺ = 425.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.89 (s, 1H), 8.36 (br s, 3H), 8.29 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 1.6, 8.4 Hz, 1H), 4.40 (br s, 2H), 3.78 (s, 3H)
4-149		4B	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)quinoline-5-carbonitrile LCMS [M+1] ⁺ = 408.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 9.20 (dd, J = 1.6, 4.0 Hz, 1H), 8.58 - 8.52 (m, 2H), 8.33 (s, 1H), 8.30 (br s, 3H), 8.06 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 4.0, 8.4 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.39 (dd, J = 1.2, 8.4 Hz, 1H), 4.39 - 4.19 (m, 2H), 3.80 (s, 3H)
4-150		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chloro-4-methylbenzonitrile LCMS [M+1] ⁺ = 405.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.23 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.77 (d, J = 1.2 Hz, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 7.52 (dd, J = 1.2, 8.0 Hz, 1H), 4.51 - 4.37 (m, 2H), 3.82 (s, 3H), 2.53 (s, 3H)
4-151		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chloro-5-methylbenzonitrile LCMS [M+1] ⁺ = 405.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.53 - 8.33 (m, 3H), 8.28 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.45 (br d, J = 8.4 Hz, 1H), 4.23 (d, J = 12 Hz, 2H), 3.75 (s, 3H), 3.33 (br s, 3H)
4-152		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluorobenzonitrile LCMS [M+1] ⁺ = 375.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.39 (br s, 3H), 8.35 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.01 - 7.95 (m, 1H), 7.94 - 7.87 (m, 2H), 7.74 (s,

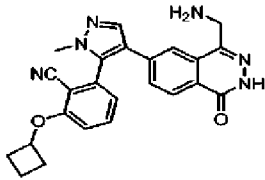
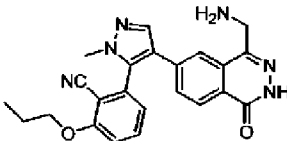
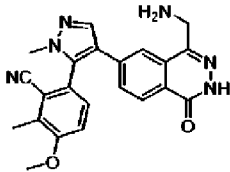
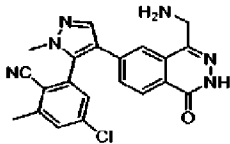
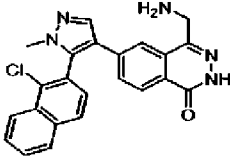
				1H), 7.45 (br d, J = 8.4 Hz, 1H), 4.30 (br d, J = 7.2 Hz, 2H), 3.77 (s, 3H)
4-153		4B	4-4	4-(aminomethyl)-6-(5-(2-(difluoromethyl)phenyl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 382.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.82 (s, 1H), 8.34 (br s, 3H), 8.28 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.87 - 7.83 (m, 1H), 7.82 - 7.78 (m, 2H), 7.63 - 7.58 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H), 6.77 - 6.46 (t, J = 54.4 Hz, 1H), 4.21 - 4.13 (m, 2H), 3.60 (s, 3H)
4-154		4B	4-4	4-(aminomethyl)-6-(5-((2-chlorobenzyl)oxy)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 396.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.47 - 8.29 (br s, 3H), 8.24 (d, J = 8.4 Hz, 1H), 8.07 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.50 - 7.45 (m, 2H), 7.38 (dt, J = 2.0, 7.6 Hz, 1H), 7.36 - 7.30 (dt, J = 2.0, 7.6 Hz, 1H), 5.16 (s, 2H), 4.45 (s, 2H), 3.63 (s, 3H)
4-155		4B	4-4	4-(aminomethyl)-6-(5-((3-chlorobenzyl)oxy)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 396.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.43 - 8.30 (br s, 3H), 8.25 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 1.6, 8.4 Hz, 1H), 8.02 (s, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.40 - 7.35 (m, 3H), 5.08 (s, 2H), 4.45 (s, 2H), 3.67 (s, 3H)
4-156		4B	4-4	4-(aminomethyl)-6-(5-((4-chlorobenzyl)oxy)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 396.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.53 - 8.32 (br s, 3H), 8.26 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 1.6, 8.4 Hz, 1H), 8.03 (s, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.44 - 7.39 (m, 4H), 5.07 (s, 2H), 4.47 (br s, 2H), 3.65 (s, 3H)

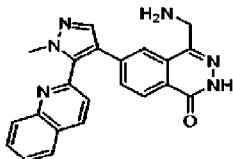
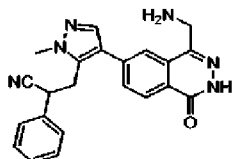
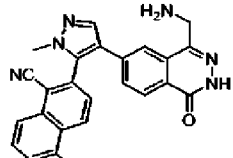
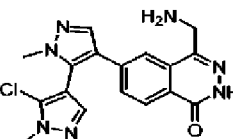
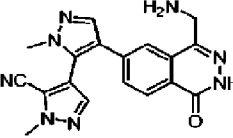
4-157		4B	4-5	2-(((4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)benzonitrile LCMS [M+1] ⁺ = 387.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.57 - 8.34 (m, 3H), 8.23 (d, J = 8.4 Hz, 1H), 8.07 - 8.00 (m, 2H), 7.91 (s, 1H), 7.84 (br d, J = 7.6 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.66 - 7.61 (m, 1H), 7.54 (br t, J = 7.6 Hz, 1H), 5.22 (s, 2H), 4.46 (br s, 2H), 3.69 (s, 3H)
4-158		4B	4-6	4-(aminomethyl)-6-(5-ethoxypyrazolo[1,5-a]pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 322.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.68 (d, J = 7.6 Hz, 1H), 8.62 (s, 1H), 8.59 (br s, 3H), 8.34 - 8.29 (d, J = 8.4 Hz, 1H), 8.27 - 8.23 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 2.4, 7.6 Hz, 1H), 4.58 (br d, J = 5.6 Hz, 2H), 3.96 (s, 3H)
4-159		4A	4-7	4-(aminomethyl)-6-(5-(methyl(phenyl)amino)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 358.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.00 (s, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.43 (br s, 3H), 8.38 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H), 8.26 - 8.19 (m, 2H), 7.84 (t, J = 2.4 Hz, 1H), 7.47 - 7.38 (m, 2H), 7.24 (dd, J = 0.8, 8.4 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 4.60 (br d, J = 5.6 Hz, 2H), 3.42 (s, 3H)
4-160		4A	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-methoxybenzonitrile LCMS [M+1] ⁺ = 387.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.50 - 8.35 (br s, 3H), 8.26 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.70 - 7.66 (m, 2H), 7.49 (dd, J = 2.8, 8.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.40 - 4.22 (m, 2H), 3.92 (s, 3H), 3.72 (s, 3H)
4-161		4B	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-cyclopropylbenzonitrile LCMS [M+1] ⁺ = 397.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.36 (br s, 3H), 8.27 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.48 (s, 1H), 7.47 - 7.44 (dd, J = 8.4, 2.0 Hz, 1H), 7.43 (dd, J = 1.6, 8.4 Hz, 1H), 4.27 (br s, 2H), 3.72 (s, 3H), 2.15 - 2.07 (m, 1H), 1.12 (dd, J = 2.8, 8.4 Hz, 2H), 0.95 - 0.81 (m, 2H)

4-162		4A	4-1	4-(aminomethyl)-6-(5-(2,4-dimethoxyphenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 405.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.99 (s, 1H), 8.84 (d, J = 1.6 Hz, 1H), 8.51 (br s, 3H), 8.37 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 1.2 Hz, 1H), 8.21 (dd, J = 1.6, 8.4 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.87 (t, J = 2.0 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.59 (dd, J = 2.8, 8.8 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H), 3.80 - 3.79 (s, 3H), 3.76 (s, 3H)
4-163		4B	4-5	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile LCMS [M+1] ⁺ = 393.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.95 (s, 1H), 12.46 (d, J = 2.4 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.48 - 8.38 (m, 3H), 8.37 - 8.30 (m, 2H), 8.28 (s, 1H), 8.03 (d, J = 2.8 Hz, 1H), 7.97 (d, J = 6.8 Hz, 1H), 7.91 - 7.85 (m, 1H), 7.84 - 7.78 (m, 1H), 7.54 (dt, J = 1.2, 7.6 Hz, 1H), 4.62 (br s, 2H)
4-164		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4,5-dichlorobenzonitrile LCMS [M+1] ⁺ = 424.9; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.52 (br s, 3H), 8.49 (s, 1H), 8.31 (s, 1H), 8.24 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.40 (dd, J = 1.6, 8.4 Hz, 1H), 4.39 (br t, J = 5.2 Hz, 2H), 3.78 (s, 3H)
4-165		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4,6-dichlorobenzonitrile LCMS [M+1] ⁺ = 425.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.90 (s, 1H), 8.46 - 8.31 (br s, 3H), 8.28 (s, 1H), 8.28 - 8.26 (m, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 4.46 - 4.30 (m, 2H), 3.79 (s, 3H)
4-166		4B	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)quinoline-7-carbonitrile LCMS [M+1] ⁺ = 408.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 9.18 (dd, J = 1.6, 4.4 Hz, 1H), 8.82 (s, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 8.33 - 8.23 (m, 3H), 8.03 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 1.2 Hz, 1H), 7.83 (dd, J = 4.4, 8.4 Hz, 1H), 7.40 (dd, J = 1.6, 8.4 Hz, 1H), 4.33 - 4.23 (m, 2H), 3.78 (s, 3H)

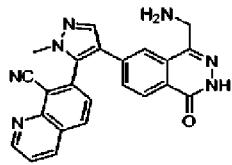
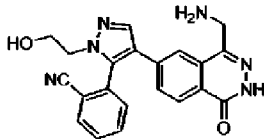
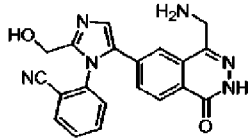
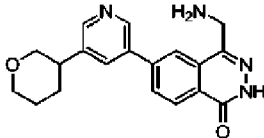
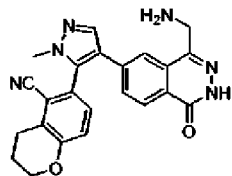
4-167		4B	4-4	7-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)quinoline-6-carbonitrile LCMS [M+1] ⁺ = 408.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 9.17 (dd, J = 1.6, 4.4 Hz, 1H), 8.90 (s, 1H), 8.62 (d, J = 7.6 Hz, 1H), 8.40 (s, 1H), 8.36 - 8.25 (m, 4H), 8.02 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 1.2 Hz, 1H), 7.83 (dd, J = 4.4, 8.4 Hz, 1H), 7.37 (dd, J = 1.6, 8.4 Hz, 1H), 4.30 (br t, J = 5.6 Hz, 2H), 3.80 (s, 3H)
4-168		4B	4-5	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-methoxybenzonitrile LCMS [M+1] ⁺ = 421.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.88 (s, 1H), 8.39 (br s, 3H), 8.26 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.48 - 4.25 (m, 2H), 4.01 (s, 3H), 3.75 (s, 3H)
4-169		4B	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chloro-4-methoxybenzonitrile LCMS [M+1] ⁺ = 421.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.60 (br s, 3H), 8.32 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 4.40 - 4.22 (m, 2H), 3.96 (s, 3H), 3.76 (s, 3H)
4-170		4B	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-chloro-3-methoxybenzonitrile LCMS [M+1] ⁺ = 421.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.37 (br s, 3H), 8.27 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 1.2, 8.4 Hz, 1H), 4.43 - 4.29 (m, 2H), 4.04 (s, 3H), 3.73 (s, 3H)
4-171		4B	4-8	4-(aminomethyl)-6-(5-(dimethylamino)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 299.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.43 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.86 - 8.92 (m, 1H), 7.77 (s, 1H), 4.03 (s, 2H), 3.74 (s, 3H), 2.80 (s, 6H), 2.12 - 2.31 (m, 2H)

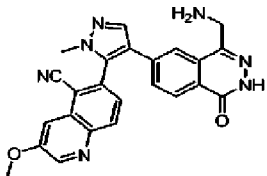
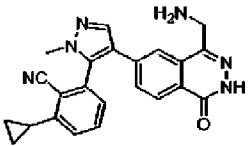
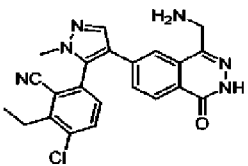
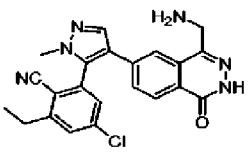
4-172		4B	4-8	N-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-N-methylbenzamide LCMS [M+1] ⁺ = 389.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.47 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.63 - 7.72 (m, 1H), 7.19 - 7.31 (m, 1H), 7.02 - 7.12 (m, 2H), 6.83 - 6.93 (m, 2H), 3.99 (s, 2H), 3.83 (s, 3H), 3.45 (s, 3H), 1.80 - 2.24 (m, 2H).
4-173		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-ethoxybenzonitrile LCMS [M+1] ⁺ = 401.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.37 (br s, 3H), 8.25 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 2.8 Hz, 1H), 7.46 (dd, J = 2.8, 8.8 Hz, 1H), 7.42 (dd, J = 1.6, 8.4 Hz, 1H), 4.39 - 4.27 (m, 2H), 4.19 (q, J = 6.8 Hz, 2H), 3.71 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H)
4-174		4B	4-5	2-(((4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)-3-chlorobenzonitrile LCMS [M+1] ⁺ = 421.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.44 (br s, 3H), 8.18 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.89 (dd, J = 1.6, 8.4 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.63 - 7.59 (m, 1H), 7.55 (dd, J = 1.6, 7.2 Hz, 1H), 5.23 (s, 2H), 4.46 (s, 2H), 3.75 (s, 3H)
4-175		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxybenzonitrile LCMS [M+1] ⁺ = 413.0; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.41 - 8.29 (br s, 3H), 8.26 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.93 - 7.88 (m, 1H), 7.75 - 7.71 (m, 2H), 7.44 (dd, J = 1.6, 8.4 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 4.29 (m, 2H), 4.13 (tt, J = 2.8, 6.4 Hz, 1H), 3.72 (s, 3H), 0.91 - 0.78 (m, 4H)
4-176		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-isopropoxybenzonitrile LCMS [M+1] ⁺ = 415.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.41 (br s, 3H), 8.27 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 7.6, 8.8 Hz, 1H), 7.79 (d, J = 0.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.42 (dd, J = 1.2, 8.0 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 4.89 (td, J = 6.0, 12.0 Hz, 1H), 4.39 - 4.23 (m, 2H), 3.72 (s, 3H), 1.34 (dd, J = 1.2, 6.0 Hz, 6H)

4-177		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclobutoxybenzonitrile LCMS [M+1] ⁺ = 427.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.38 (br s, 3H), 8.26 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 7.6, 8.4 Hz, 1H), 7.75 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 4.93 (t, J = 7.2 Hz, 1H), 4.38 - 4.21 (m, 2H), 3.72 (s, 3H), 2.55 - 2.51 (m, 2H), 2.21 - 2.05 (m, 2H), 1.83 (q, J = 10.2 Hz, 1H), 1.75 - 1.59 (m, 1H)
4-178		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-propoxybenzonitrile LCMS [M+1] ⁺ = 415.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.86 (s, 1H), 8.59 (br s, 3H), 8.31 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 8.0, 8.4 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 4.30 - 4.13 (m, 4H), 3.72 (s, 3H), 1.77 (q, J = 7.6 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H)
4-179		4B	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-methoxy-2-methylbenzonitrile LCMS [M+1] ⁺ = 401.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.35 (br s, 3H), 8.26 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 9.6 Hz, 1H), 4.37 - 4.26 (m, 2H), 3.96 (s, 3H), 3.69 (s, 3H), 2.39 (s, 3H)
4-180		4B	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-methylbenzonitrile LCMS [M+1] ⁺ = 405.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 (s, 1H), 8.37 (br s, 3H), 8.28 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 1.6, 7.2 Hz, 2H), 7.46 (dd, J = 1.6, 8.4 Hz, 1H), 4.36 - 4.26 (m, 2H), 3.74 (s, 3H), 2.54 (s, 3H)
4-181		4D	4-4	4-(aminomethyl)-6-(5-(1-chloronaphthalen-2-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 416.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.82 (s, 1H), 8.38 - 8.26 (m, 5H), 8.21 - 8.11 (m, 2H), 7.99 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.83 - 7.77 (m, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 1.5, 8.0 Hz, 1H), 4.44 - 4.23 (m, 2H), 3.67 (s, 3H)

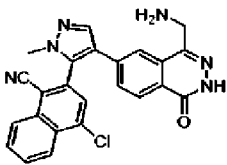
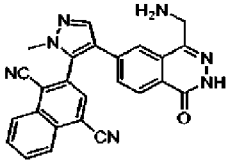
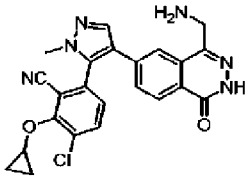
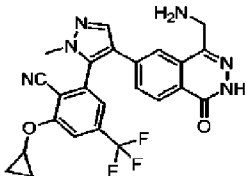
4-182		4D	4-4	4-(aminomethyl)-6-(1-methyl-5-(quinolin-2-yl)-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 383.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.45 (s, 1H), 8.40 (br s, 3H), 8.16 - 8.11 (m, 2H), 8.10 - 8.04 (m, 2H), 7.98 (d, <i>J</i> = 1.2 Hz, 1H), 7.87 (dt, <i>J</i> = 1.2, 7.6 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.53 (dd, <i>J</i> = 1.2, 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 8.4 Hz, 1H), 4.36 (br d, <i>J</i> = 4.8 Hz, 2H), 3.99 (s, 3H)
4-183		4D	4-4	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-phenylpropanenitrile LCMS [M+1] ⁺ = 385.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.90 (s, 1H), 8.47 (br d, <i>J</i> = 14.0 Hz, 3H), 8.23 (d, <i>J</i> = 8.4 Hz, 1H), 7.85 (d, <i>J</i> = 8.4 Hz, 1H), 7.81 (s, 1H), 7.75 (d, <i>J</i> = 1.2 Hz, 1H), 7.27 - 7.21 (m, 3H), 7.21 - 7.14 (m, 2H), 4.65 - 4.45 (m, 2H), 4.42 (t, <i>J</i> = 7.6 Hz, 1H), 3.82 (s, 3H), 3.76 - 3.67 (m, 1H), 3.66 - 3.57 (m, 1H)
4-184		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-chloro-1-naphthonitrile LCMS [M+1] ⁺ = 441.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 8.70 (d, <i>J</i> = 8.8 Hz, 1H), 8.54 - 8.39 (m, 3H), 8.38 - 8.34 (m, 1H), 8.16 (d, <i>J</i> = 8.4 Hz, 1H), 8.04 (d, <i>J</i> = 7.6 Hz, 1H), 8.02 - 7.93 (m, 3H), 7.90 - 7.85 (m, 1H), 7.36 - 7.24 (m, 1H), 4.34 (br s, 2H), 3.78 (s, 3H)
4-185		4D		4-(aminomethyl)-6-(5'-chloro-1',2-dimethyl-1H,2H-[3,4'-bipyrazol]-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 370.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.43 - 8.30 (br s, 3H), 8.19 (s, 1H), 8.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.92 (s, 1H), 7.81 (d, <i>J</i> = 1.2 Hz, 1H), 7.68 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.40 - 4.32 (m, 2H), 3.90 (s, 3H), 3.74 (s, 3H)
4-186		4D		4-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1',2-dimethyl-1H,2H-[3,4'-bipyrazole]-5'-carbonitrile LCMS [M+1] ⁺ = 361.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.89 (s, 1H), 8.40 - 8.31 (br s, 3H), 8.19 - 8.17 (m, 2H), 8.10 (s, 1H), 7.83 (d, <i>J</i> = 1.2 Hz, 1H), 7.67 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.42 - 4.34 (m, 2H), 4.09 (s, 3H), 3.83 (s, 3H)

4-187		4D		4-(aminomethyl)-6-(1'-benzyl-5'-chloro-2-methyl-1H,2H-[3,4'-bipyrazol]-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 446.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.50 (br s, 3H), 8.21 (s, 1H), 8.07 (d, <i>J</i> = 8.4 Hz, 1H), 8.05 (s, 1H), 7.89 (d, <i>J</i> = 1.2 Hz, 1H), 7.53 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 7.42 - 7.27 (m, 3H), 7.19 - 7.11 (m, 2H), 5.48 (s, 2H), 4.44 - 4.31 (m, 2H), 3.75 (s, 3H).
4-188		4D		2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxybenzonitrile LCMS [M+1] ⁺ = 447.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.87 (s, 1H), 8.53 (br s, 3H), 8.28 (s, 1H), 8.12 (d, <i>J</i> = 8.4 Hz, 1H), 7.80 (d, <i>J</i> = 1.8 Hz, 2H), 7.51 (d, <i>J</i> = 1.8 Hz, 1H), 7.44 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.48 - 4.26 (m, 2H), 4.21 (td, <i>J</i> = 3.2, 6.0 Hz, 1H), 3.74 (s, 3H), 0.98 - 0.87 (m, 2H), 0.86 - 0.73 (m, 2H)
4-189*		4D	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-propylbenzonitrile LCMS [M+1] ⁺ = 399.2; ¹ H NMR (400 MHz, CD ₃ OD- <i>d</i> ₄) δ = 8.19 - 8.13 (m, 2H), 7.87 - 7.81 (m, 1H), 7.74 (s, 1H), 7.67 (d, <i>J</i> = 8.0 Hz, 1H), 7.58 (d, <i>J</i> = 7.6 Hz, 1H), 7.51 - 7.45 (m, 1H), 4.48 - 4.32 (m, 2H), 3.80 (s, 3H), 2.90 - 2.83 (m, 2H), 1.74 - 1.63 (m, 2H) 0.97 - 0.91 (m, 3H)
4-190		4B	4-6	4-(aminomethyl)-6-(3-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 368.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.94 (s, 1H), 12.19 (br d, <i>J</i> = 7.2 Hz, 1H), 8.85 (s, 1H), 8.71 (s, 1H), 8.57 (br d, <i>J</i> = 1.2 Hz, 3H), 8.38 (s, 2H), 8.31 (br s, 1H), 7.99 (d, <i>J</i> = 2.4 Hz, 1H), 7.84 (d, <i>J</i> = 7.6 Hz, 2H), 7.47 (t, <i>J</i> = 7.6 Hz, 2H), 7.29 (t, <i>J</i> = 7.2 Hz, 1H), 4.63 (br s, 2H)
4-191		4B	4-4	4-(aminomethyl)-6-(6-phenylimidazo[1,2-b]pyridazin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 369.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.98 (s, 1H), 8.88 (d, <i>J</i> = 1.2 Hz, 1H), 8.78 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 8.67 (s, 1H), 8.50 (br s, 3H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.41 (d, <i>J</i> = 9.6 Hz, 1H), 8.22 (d, <i>J</i> = 7.2 Hz, 2H), 8.02 (d, <i>J</i> = 9.6 Hz, 1H), 7.71 - 7.57 (m, 3H), 4.63 (br s, 2H)

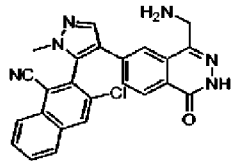
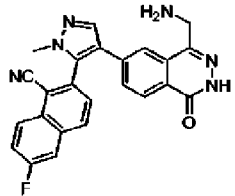
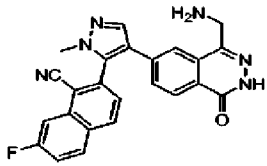
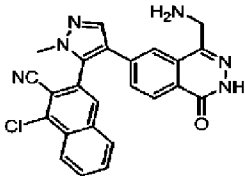
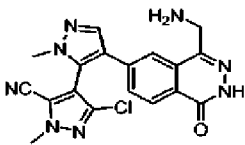
4-192		4D	4-9	7-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)quinoline-8-carbonitrile LCMS [M+1] ⁺ = 408.2; ¹ H NMR (400 MHz, CD ₃ OD) δ = 9.09 (dd, <i>J</i> = 1.6, 4.0 Hz, 1H), 8.59 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 8.47 (d, <i>J</i> = 8.4 Hz, 1H), 8.17 (s, 1H), 8.12 (d, <i>J</i> = 8.4 Hz, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 1H), 7.84 (s, 1H), 7.79 (dd, <i>J</i> = 4.4, 8.4 Hz, 1H), 7.46 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.46 - 4.30 (m, 2H), 3.88 (s, 3H)
4-193		4D	4-2	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-(2-hydroxyethyl)-1H-pyrazol-5-yl)benzonitrile LCMS [M+1] ⁺ = 387.3; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.50 - 12.33 (br s, 1H), 8.24 (s, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 8.04 (d, <i>J</i> = 7.2 Hz, 1H), 7.98 - 7.92 (m, 1H), 7.85 - 7.76 (m, 2H), 7.65 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 7.54 (s, 1H), 4.98 - 4.76 (m, 1H), 4.08 - 4.01 (br s, 1H), 3.99 - 3.92 (m, 1H), 3.79 - 3.73 (m, 1H), 3.70 - 3.65 (m, 1H), 3.63 (br s, 2H)
4-194		4D	4-2	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-2-(hydroxymethyl)-1H-imidazol-1-yl)benzonitrile LCMS [M+1] ⁺ = 373.3; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.91 (s, 1H), 8.50 - 8.33 (br s, 3H), 8.13 (d, <i>J</i> = 8.8 Hz, 1H), 8.00 - 7.93 (m, 3H), 7.75 (ddd, <i>J</i> = 2.8, 6.4, 7.6 Hz, 1H), 7.69 (s, 1H), 7.58 - 7.50 (m, 2H), 5.37 (t, <i>J</i> = 5.6 Hz, 1H), 4.46 (br d, <i>J</i> = 5.6 Hz, 1H), 4.34 (dd, <i>J</i> = 5.6, 13.2 Hz, 1H), 4.26 - 4.18 (m, 1H), 4.04 (br d, <i>J</i> = 16.0 Hz, 1H)
4-195		4D	4-4	4-(aminomethyl)-6-(5-(tetrahydro-2H-pyran-3-yl)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 337.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.07 (d, <i>J</i> = 2.0 Hz, 1H), 8.69 (d, <i>J</i> = 2.0 Hz, 1H), 8.49 (br s, 3H), 8.40 (d, <i>J</i> = 2.0 Hz, 1H), 8.34 (t, <i>J</i> = 1.6 Hz, 1H), 8.32 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 8.28 (s, 1H), 4.62 (br d, <i>J</i> = 5.6 Hz, 2H), 3.98 - 3.85 (m, 2H), 3.56 - 3.40 (m, 2H), 3.09 - 2.90 (m, 1H), 2.07 - 1.86 (m, 2H), 1.74 - 1.63 (m, 2H)
4-196		4D	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)chromane-5-carbonitrile LCMS [M+1] ⁺ = 435.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.85 (s, 1H), 8.39 (br s, 3H), 8.25 (s, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.72 (d, <i>J</i> = 1.2 Hz, 1H), 7.50 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 7.42 (d, <i>J</i> = 8.4 Hz, 1H), 7.28 (d, <i>J</i> = 8.4 Hz, 1H), 4.33 - 4.22 (m, 4H), 3.70 (s, 3H),

				2.90 (br t, $J = 6.4$ Hz, 2H), 2.07 - 1.98 (m, 2H)
4-197		4D	4-4	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-methoxyquinoline-5-carbonitrile LCMS $[M+1]^+ = 438.2$; ^1H NMR (500 MHz, CD_3OD) $\delta = 8.86$ (d, $J = 3.0$ Hz, 1H), 8.48 (d, $J = 8.5$ Hz, 1H), 8.19 (s, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.85 (d, $J = 8.5$ Hz, 1H), 7.77 (s, 1H), 7.73 (d, $J = 2.5$ Hz, 1H), 7.55 - 7.49 (m, 1H), 4.50 - 4.20 (m, 2H), 4.05 (s, 3H), 3.87 (s, 3H)
4-198		4E	4-2	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropylbenzonitrile LCMS $[M+1]^+ = 397.3$; ^1H NMR (400 MHz, CD_3OD) $\delta = 8.23$ (d, $J = 8.4$ Hz, 1H), 8.14 (s, 1H), 7.81 - 7.75 (m, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.57 (s, 1H), 7.50 - 7.45 (m, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 3.85 (s, 2H), 3.80 (s, 3H), 2.36 - 2.19 (m, 1H), 1.24 - 1.17 (m, 2H), 0.98 - 0.86 (m, 2H)
4-199		4D	4-4 4-11	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-chloro-2-ethylbenzonitrile LCMS $[M+1]^+ = 419.1$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 12.83$ (br s, 1H), 8.28 (s, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 1.2$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.41 (dd, $J = 1.2, 8.4$ Hz, 1H), 4.36 - 4.20 (m, 2H), 3.74 (s, 3H), 2.95 (q, $J = 7.6$ Hz, 2H), 1.17 (t, $J = 7.6$ Hz, 3H)
4-200		4D	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-ethylbenzonitrile LCMS $[M+1]^+ = 419.2$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 12.88$ (s, 1H), 8.38 (br s, 3H), 8.28 (s, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 2.0$ Hz, 1H), 7.82 (d, $J = 2.0$ Hz, 1H), 7.75 (d, $J = 1.2$ Hz, 1H), 7.42 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.39 - 4.22 (m, 2H), 3.75 (s, 3H), 2.83 (q, $J = 7.6$ Hz, 2H), 1.21 (t, $J = 7.6$ Hz, 3H)

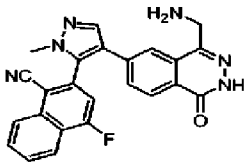
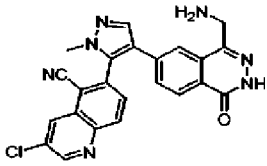
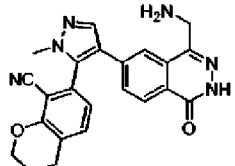
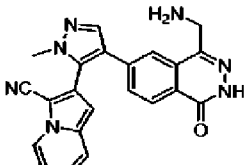
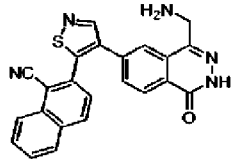
4-201		4D	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethyl-5-methoxybenzonitrile LCMS [M+1] ⁺ = 415.3; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.85 (s, 1H), 8.40 (br d, <i>J</i> = 9.6 Hz, 3H), 8.26 (s, 1H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 7.77 (s, 1H), 7.62 - 7.55 (m, 1H), 7.53 - 7.47 (m, 1H), 7.41 (d, <i>J</i> = 8.4 Hz, 1H), 4.40 - 4.19 (m, 2H), 3.97 (s, 3H), 3.71 (s, 3H), 2.80 (q, <i>J</i> = 7.6 Hz, 2H), 1.12 (t, <i>J</i> = 7.6 Hz, 3H)
4-202		4D	4-1 4-10	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethyl-4-methoxybenzonitrile LCMS [M+1] ⁺ = 415.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.85 (br s, 1H), 8.47 - 8.15 (m, 4H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.73 (d, <i>J</i> = 0.8 Hz, 1H), 7.50 (dd, <i>J</i> = 1.2, 8.4 Hz, 1H), 7.26 (d, <i>J</i> = 2.4 Hz, 1H), 7.20 (d, <i>J</i> = 2.4 Hz, 1H), 4.36 - 4.16 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 2.80 (q, <i>J</i> = 7.6 Hz, 2H), 1.22 (t, <i>J</i> = 7.6 Hz, 3H)
4-203		4E	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.2; ¹ H NMR (400 MHz, CD ₃ OD) δ = 8.28 (d, <i>J</i> = 10.0 Hz, 1H), 8.23 (s, 1H), 8.18 (br dd, <i>J</i> = 3.6, 5.2 Hz, 2H), 8.14 (d, <i>J</i> = 8.4 Hz, 1H), 7.86-7.79 (m, 3H), 7.46 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 4.47-4.31 (m, 2H), 3.86 (s, 3H). ¹⁹ F NMR (471 MHz, CD ₃ OD) δ = -116.45 (s, 1F)
4-204		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-methoxy-1-naphthonitrile LCMS [M + 1] ⁺ = 437.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.64 (d, <i>J</i> = 8.8 Hz, 1H), 8.51 (br s, 3H), 8.37 (s, 1H), 7.99 (d, <i>J</i> = 8.4 Hz, 1H), 7.96 (d, <i>J</i> = 1.2 Hz, 1H), 7.84 - 7.78 (m, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.30 (d, <i>J</i> = 8.0 Hz, 1H), 7.27 (dd, <i>J</i> = 1.2, 8.4 Hz, 1H), 4.34 (br dd, <i>J</i> = 5.6, 10.0 Hz, 2H), 4.07 (s, 3H), 3.76 (s, 3H)
4-205		4D	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-methoxy-1-naphthonitrile LCMS [M+1] ⁺ = 437.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.39 (d, <i>J</i> = 8.4 Hz, 1H), 8.33 (s, 4H), 8.07 - 8.01 (m, 2H), 7.92 (d, <i>J</i> = 1.2 Hz, 1H), 7.88 (ddd, <i>J</i> = 1.2, 7.2, 8.4 Hz, 1H), 7.80 (dt, <i>J</i> = 1.2, 7.6 Hz,

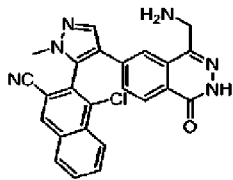
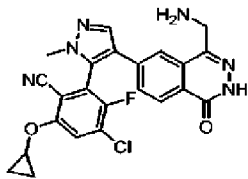
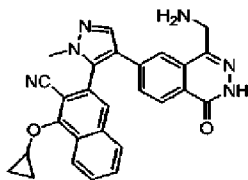
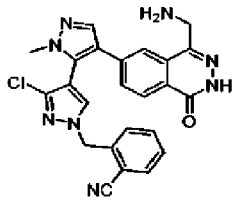
				1H), 7.41 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.35 (s, 1H), 4.43 - 4.23 (m, 2H), 4.12 (s, 3H), 3.80 (s, 3H)
4-206		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-1-naphthonitrile LCMS $[M+1]^+ = 444.1$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.84$ (s, 1H), 8.57 (br s, 3H), 8.49 - 8.44 (m, 1H), 8.38 (s, 1H), 8.23 - 8.19 (m, 1H), 8.16 (s, 1H), 8.04 - 8.00 (m, 2H), 7.99 (s, 2H), 7.32 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.45 - 4.20 (m, 2H), 3.81 (s, 3H)
4-207		4D	4-4	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)naphthalene-1,4-dicarbonitrile LCMS $[M+1]^+ = 432.2$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.84$ (s, 1H), 8.64 (s, 1H), 8.53 (br s, 3H), 8.42 - 8.37 (m, 2H), 8.27 (d, $J = 7.6$ Hz, 1H), 8.13 - 8.07 (m, 1H), 8.07 - 8.02 (m, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 1.6$ Hz, 1H), 7.35 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.42 - 4.21 (m, 2H), 3.82 (s, 3H)
4-208		4D	4-1	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-chloro-2-cyclopropoxybenzonitrile LCMS $[M+1]^+ = 447.0$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.90$ (s, 1H), 8.37 (br s, 3H), 8.27 (s, 1H), 8.12 (dd, $J = 8.4, 17.6$ Hz, 2H), 7.83 (d, $J = 0.8$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 1.2, 8.0$ Hz, 1H), 4.47 (tt, $J = 2.8, 6.0$ Hz, 1H), 4.43 - 4.27 (m, 2H), 3.78 (s, 3H), 0.88 - 0.80 (m, 1H), 0.79 - 0.70 (m, 1H), 0.65 (td, $J = 2.8, 6.0$ Hz, 2H)
4-209		4D	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-(trifluoromethyl)benzonitrile LCMS $[M+1]^+ = 481.2$; ^1H NMR (500 MHz, DMSO-d_6) $\delta = 12.88$ (s, 1 H), 8.55 (br s, 3 H), 8.33 (s, 1 H), 8.11 (d, $J = 8.4$ Hz, 1 H), 7.98 (s, 1 H), 7.84 - 7.77 (m, 2 H), 7.41 (dd, $J = 8.5, 1.5$ Hz, 1 H), 4.38-4.29 (m, 3 H), 3.76 (s, 3 H), 0.98-0.91 (m, 2 H), 0.89-0.79 (m, 2 H)

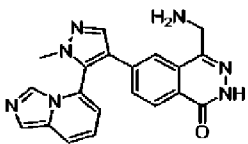
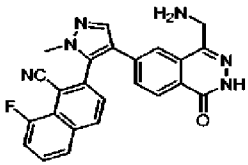
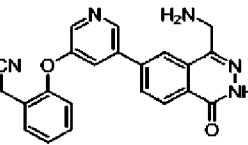
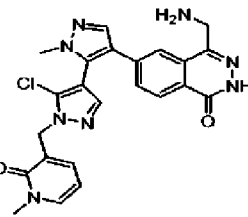
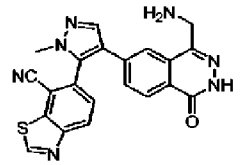
4-210		4E	4-1	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.2; ¹ H NMR (500 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.53 (d, J = 18.5 Hz, 3H), 8.44 (d, J = 6.5 Hz, 1H), 8.35 - 8.31 (m, 1H), 8.29 - 8.23 (m, 2H), 8.06 - 7.97 (m, 3H), 7.90 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 4.37 (s, 2H), 3.82 (s, 3H)
4-211		4D	4-6	4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1'-benzyl-2-methyl-1H,2H-[3,4'-bipyrazole]-5'-carbonitrile LCMS [M+1] ⁺ = 437.1; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.89 (s, 1H), 8.48 (br s, 3H), 8.25 (s, 1H), 8.19 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.49 (dd, J = 1.6, 8.4 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.24 - 7.20 (m, 2H), 5.62 (s, 2H), 4.41 - 4.32 (m, 2H), 3.84 (s, 3H)
4-212		4D	4-6	4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1'-benzyl-2-methyl-1H,2H-[3,4'-bipyrazole]-3'-carbonitrile LCMS [M+1] ⁺ = 437.3; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.89 (s, 1H), 8.63 (s, 1H), 8.48 (br s, 3H), 8.20 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 1.2 Hz, 1H), 7.56 (dd, J = 1.5, 8.4 Hz, 1H), 7.45 - 7.36 (m, 3H), 7.36 - 7.30 (m, 2H), 5.58 (s, 2H), 4.38 (br s, 2H), 3.81 (s, 3H)
4-213		4D	4-1	4-(aminomethyl)-6-(3'-chloro-2-methyl-1'-phenyl-1H,2H-[3,4'-bipyrazol]-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 432.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.84 (s, 1H), 8.44 - 8.26 (m, 4H), 7.89 (t, J = 8.0 Hz, 1H), 7.61 (br d, J = 4.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.40 (br d, J = 2.8 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 4.37 - 4.27 (m, 2H), 4.25 - 4.06 (m, 2H), 3.72 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H)
4-214		4D	4-1	4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-2-methyl-1'-phenyl-1H,2H-[3,4'-bipyrazole]-3'-carbonitrile LCMS [M+1] ⁺ = 423.2; ¹ H NMR (500 MHz, DMSO-d ₆) δ 12.90 (s, 1H), 9.36 (s, 1H), 8.56 (br s, 3H), 8.28 (s, 1H), 8.20-8.17 (m, 1H), 8.03-7.98 (m, 3H), 7.70 (dd, J = 1.6, 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 2H), 7.55-7.50 (m, 1H), 4.41 (q, J = 5.6 Hz, 2H), 3.92 (s, 3H)

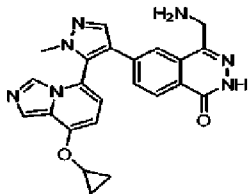
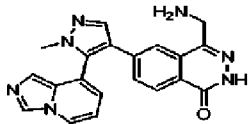
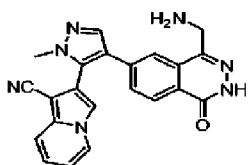
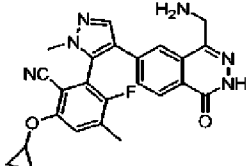
4-215		4E	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-chloro-1-naphthonitrile LCMS [M+1] ⁺ = 441.3; ¹ H NMR (400 MHz, CD ₃ OD) δ = 8.67 (s, 1H), 8.27 (s, 1H), 8.23 - 8.18 (m, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.91 - 7.85 (m, 2H), 7.84 (s, 1H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 4.55 - 4.30 (m, 2H), 3.82 (s, 3H)
4-216		4D	4-12	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.1; ¹ H NMR (400MHz, DMSO-d ₆) δ = 12.37 (br s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.26 (s, 1H), 8.20 (dd, J = 5.2, 9.2 Hz, 1H), 8.12 (dd, J = 2.4, 9.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.80 (dt, J = 2.4, 8.8 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.60 (dd, J = 1.6, 8.4 Hz, 1H), 3.78 (s, 3H), 3.54 (s, 2H)
4-217		4D	4-1	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-7-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.0; ¹ H NMR (400MHz, DMSO-d ₆) δ = 12.83 (s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.52 - 8.38 (m, 4H), 8.36 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.81 (dd, J = 8.8, 17.2 Hz, 3H), 7.35 (dd, J = 1.6, 8.4 Hz, 1H), 4.37 - 4.17 (m, 2H), 3.78 (s, 3H)
4-218		4D	4-1	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-chloro-2-naphthonitrile LCMS [M+1] ⁺ = 441.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.85 (s, 1H), 8.47 - 8.39 (m, 5H), 8.37 (s, 1H), 8.26 - 8.20 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.01 - 7.92 (m, 3H), 7.38 (dd, J = 1.2, 8.4 Hz, 1H), 4.43 - 4.28 (m, 2H), 3.79 (s, 3H)
4-219		4D	4-6	4-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-3'-chloro-1',2'-dimethyl-1'H,2H-[3,4'-bipyrazole]-5'-carbonitrile LCMS [M+1] ⁺ = 395.2; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.89 (s, 1H), 8.55 (br d, J = 1.6 Hz, 3H), 8.34 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.61 (dd, J = 1.6, 8.0 Hz, 1H), 4.39 (br d, J = 5.2 Hz, 2H), 4.05 (s, 3H), 3.80 (s, 3H)

4-220		4D	4-6	4-(aminomethyl)-6-(5-(1,3-dihydroisobenzofuran-4-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1]⁺ = 374.1; ¹H NMR (400 MHz, MeOD) δ = ¹H NMR (400 MHz, CDCl₃) δ = 8.21 (m, <i>J</i> = 8.4 Hz, 1H), 8.15 (s, 1H), 7.71 (dd, <i>J</i> = 8.4, 1.2 Hz, 1H), 7.63 - 7.53 (m, 3H), 7.44 (d, <i>J</i> = 7.2 Hz, 1H), 5.09 - 5.18 (m, 2H), 4.80 (m, <i>J</i> = 12.4 Hz, 1H), 4.31 - 4.21 (m, 1H), 4.21 - 4.14 (m, 1H), 3.76 (s, 3H); (400 MHz, T = 353K, DMSO-<i>d</i>₆) δ = 12.65 (s, 1H), 8.51 (s, 3H), 8.19 (s, 1H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 7.60-7.51 (m, 4H), 7.41 - 7.40 (m, 1H), 5.11 - 5.09 (m, 2H), 4.77 - 4.74 (m, 1H), 4.40 - 4.34 (m, 1H), 4.11 (s, 2H), 3.73 (s, 3H)
4-221		4D	4-6	4-(aminomethyl)-6-(5-(isochroman-8-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1]⁺ = 388.1; ¹H NMR (400 MHz, MeOD) δ = 8.24 - 8.19 (m, 2H), 7.77 (dd, <i>J</i> = 1.2, 8.4 Hz, 1H), 7.52 (s, 1H), 7.51 - 7.43 (m, 2H), 7.28 (d, <i>J</i> = 6.8 Hz, 1H), 4.39 - 4.33 (m, 1H), 4.23 - 4.12 (m, 3H), 3.94 - 3.80 (m, 2H), 3.69 (s, 3H), 3.04 - 2.89 (m, 2H); (400 MHz, T = 352K, DMSO-<i>d</i>₆) δ = 12.64 (s, 1H), 8.48 (s, 3H), 8.24 (s, 1H), 8.08 (d, <i>J</i> = 8.0 Hz, 1H), 7.61 (d, <i>J</i> = 8.4 Hz, 1H), 7.56 (s, 1H), 7.47 - 7.39 (m, 2H), 7.27 - 7.22 (m, 1H), 4.33 - 4.27 (m, 1H), 4.12 - 4.05 (m, 3H), 3.91 - 3.73 (m, 2H), 3.78 (s, 3H), 3.03 - 2.84 (m, 2H)
4-222		4D	4-6	4-(aminomethyl)-6-(5-(isoquinolin-8-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1]⁺ = 383.1; ¹H NMR (400 MHz, MeOD) δ = 9.20 (s, 1H), 8.68 - 8.60 (m, 2H), 8.57 (d, <i>J</i> = 8.4 Hz, 1H), 8.44 (t, <i>J</i> = 8.0 Hz, 1H), 8.31 (s, 1H), 8.27 (d, <i>J</i> = 7.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.4 Hz, 1H), 7.77 (s, 1H), 7.39 (d, <i>J</i> = 8.4 Hz, 1H), 4.49 - 4.39 (m, 1H), 4.31 - 4.22 (m, 1H), 3.80 (s, 3H)
4-223		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-fluoro-1-naphthonitrile LCMS [M+1]⁺ = 425.1; ¹H NMR (400MHz, DMSO-<i>d</i>₆) δ = 12.85 (s, 1H), 8.61 (d, <i>J</i> = 8.4 Hz, 1H), 8.41 - 8.25 (m, 4H), 8.07 - 7.96 (m, 2H), 7.96 - 7.84 (m, 3H), 7.71 (dd, <i>J</i> = 8.0, 10.0 Hz, 1H), 7.36 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.39 - 4.20 (m, 2H), 3.80 (s, 3H)

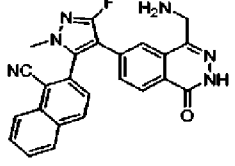
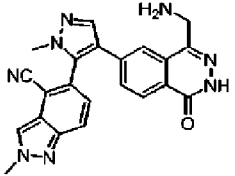
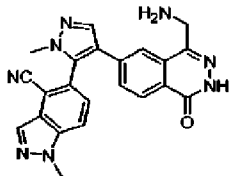
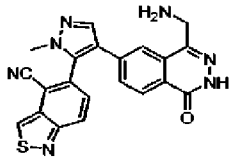
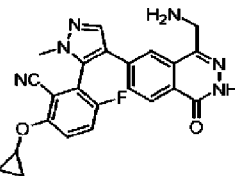
4-224		4D	4-13	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 8.44 (br s, 3H), 8.37 - 8.33 (m, 2H), 8.18 (d, <i>J</i> = 8.0 Hz, 1H), 8.04 - 7.98 (m, 2H), 7.98 - 7.95 (m, 1H), 7.95 - 7.91 (m, 2H), 7.89 (d, <i>J</i> = 10.0 Hz, 1H), 7.73 - 7.65 (m, 1H), 7.36 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.42 - 4.27 (m, 2H), 3.80 (s, 3H)
4-225		4D	4-6	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-chloroquinoline-5-carbonitrile LCMS [M + 1] ⁺ = 442.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 9.21 (d, <i>J</i> = 2.4 Hz, 1H), 8.57 (d, <i>J</i> = 8.8 Hz, 1H), 8.54 - 8.52 (m, 1H), 8.44 (br s, 3H), 8.37 (s, 1H), 8.08 (d, <i>J</i> = 8.8 Hz, 1H), 8.02 (d, <i>J</i> = 8.4 Hz, 1H), 7.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.40 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.34 - 4.19 (m, 2H), 3.80 (s, 3H)
4-226		4D	4-2	7-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)chromane-8-carbonitrile LCMS [M+1] ⁺ = 413.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.40 (br s, 1H), 8.17 (s, 1H), 8.12 (d, <i>J</i> = 8.4 Hz, 1H), 7.70 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 7.60 (d, <i>J</i> = 8.0 Hz, 1H), 7.58 (d, <i>J</i> = 1.6 Hz, 1H), 7.14 (d, <i>J</i> = 7.6 Hz, 1H), 4.35 (br t, <i>J</i> = 4.8 Hz, 2H), 3.72 (s, 3H), 3.68 (d, <i>J</i> = 2.0 Hz, 2H), 2.89 (br t, <i>J</i> = 6.0 Hz, 2H), 2.05 - 2.00 (m, 2H)
4-227		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)indolizine-3-carbonitrile LCMS [M + 1] ⁺ = 396.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 8.48 - 8.45 (m, 1H), 8.41 (br s, 3H), 8.24 (s, 1H), 8.08 (d, <i>J</i> = 8.0 Hz, 1H), 7.94 (d, <i>J</i> = 1.2 Hz, 1H), 7.80 (d, <i>J</i> = 9.2 Hz, 1H), 7.50 (dd, <i>J</i> = 1.6, 8.3 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.08 (dt, <i>J</i> = 1.2, 6.8 Hz, 1H), 6.93 (s, 1H), 4.37 (br d, <i>J</i> = 5.2 Hz, 2H), 3.84 (s, 3H)
4-228		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)isothiazol-5-yl)-1-naphthonitrile LCMS [M+1] ⁺ = 409.9; ¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ = 12.96 (s, 1H), 9.21 (s, 1H), 8.49 - 8.36 (m, 4H), 8.21 (d, <i>J</i> = 7.6 Hz, 1H), 8.17 (s, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 2H), 7.90 -

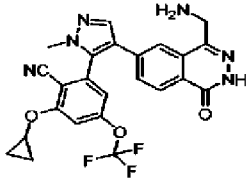
				7.77 (m, 2H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.52 (dd, $J = 1.6, 8.4$ Hz, 1H), 4.36 (s, 2H)
4-229		4D	4-6	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-2-naphthonitrile LCMS $[M+1]^+ = 441.0/443.0$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.82$ (s, 1H), 8.94 (s, 1H), 8.49 - 8.39 (m, 5H), 8.32 (d, $J = 8.0$ Hz, 1H), 8.06 - 8.00 (m, 2H), 7.99 - 7.93 (m, 2H), 7.27 (d, $J = 8.4$ Hz, 1H), 4.41 - 4.32 (m, 2H), 3.71 (s, 3H)
4-230		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile LCMS $[M+1]^+ = 465.1$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.88$ (s, 1H), 8.50 (br s, 3H), 8.37 (s, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 6.0$ Hz, 1H), 7.85 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 4.42 - 4.30 (m, 2H), 4.22 (br d, $J = 3.2$ Hz, 1H), 3.78 (s, 3H), 0.96 - 0.87 (m, 2H), 0.87 - 0.76 (m, 2H)
4-231		4D	4-6	3-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-cyclopropoxy-2-naphthonitrile LCMS $[M+1]^+ = 215.0$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.84$ (s, 1H), 8.39 (br s, 3H), 8.35 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 1H), 8.11 (d, $J = 7.6$ Hz, 1H), 8.08 - 8.02 (m, 2H), 7.96 (d, $J = 1.2$ Hz, 1H), 7.89 - 7.78 (m, 2H), 7.38 (dd, $J = 1.2, 8.4$ Hz, 1H), 4.61 (tt, $J = 2.8, 6.0$ Hz, 1H), 4.42 - 4.28 (m, 2H), 3.80 (s, 3H), 1.00 - 0.90 (m, 2H), 0.80 - 0.64 (m, 2H)
4-232		4D	4-6	2-((4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-3'-chloro-2-methyl-1'H,2H-[3,4'-bipyrazol]-1'-yl)methyl)benzonitrile LCMS $[M+1]^+ = 471.0$; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 12.86$ (s, 1H), 8.43 (s, 4H), 8.21 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.96 - 7.87 (m, 2H), 7.77 (dt, $J = 1.2, 7.6$ Hz, 1H), 7.67 - 7.55 (m, 2H), 7.49 (d, $J = 7.6$ Hz, 1H), 5.65 (s, 2H), 4.41 (br s, 2H), 3.74 (s, 3H)

4-233		4D	4-6	4-(aminomethyl)-6-(5-(imidazo[1,5-a]pyridin-5-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 372.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.72 (s, 1H), 8.39 (s, 1H), 8.07 - 7.97 (m, 3H), 7.76 (s, 1H), 7.52 - 7.38 (m, 2H), 7.35 - 7.26 (m, 1H), 4.34 - 4.11 (m, 2H), 3.82 (s, 3H)
4-234		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-8-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 425.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 8.57 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 8.47 (br s, 3H), 8.37 (s, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.90 (d, <i>J</i> = 1.2 Hz, 1H), 7.87 - 7.78 (m, 2H), 7.67 (dd, <i>J</i> = 7.6, 12.2 Hz, 1H), 7.34 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.43 - 4.21 (m, 2H), 3.76 (s, 3H)
4-235		4D	4-6	2-(2-((5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)oxy)phenyl)acetonitrile LCMS [M+1] ⁺ = 384.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.00 (s, 1H), 9.05 (d, <i>J</i> = 1.7 Hz, 1H), 8.60 (br s, 3H), 8.48 - 8.43 (m, 1H), 8.40 - 8.36 (m, 1H), 8.35 - 8.31 (m, 1H), 8.30 - 8.22 (m, 1H), 8.19 (t, <i>J</i> = 2.1 Hz, 1H), 7.57 (dd, <i>J</i> = 1.2, 7.6 Hz, 1H), 7.41 (dt, <i>J</i> = 1.5, 7.9 Hz, 1H), 7.34 - 7.18 (m, 1H), 7.09 - 7.01 (m, 1H), 4.58 (br d, <i>J</i> = 5.6 Hz, 2H), 4.11 (s, 2H)
4-236		4D	4-6	4-(aminomethyl)-6-(5'-chloro-2-methyl-1'-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1'H,2H-[3,4'-bipyrazol]-4-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 477.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.85 (s, 1H), 8.43 (s, 3H), 8.28 (s, 1H), 8.20 (s, 1H), 8.14 (d, <i>J</i> = 8.4 Hz, 1H), 7.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.75 (d, <i>J</i> = 6.8, 2.0 Hz, 1H), 7.67 (d, <i>J</i> = 8.4, 1.2 Hz, 1H), 7.36 (d, <i>J</i> = 6.8, 2.0 Hz, 1H), 6.28 (t, <i>J</i> = 6.8 Hz, 1H), 5.20 (s, 2H), 4.41 (d, <i>J</i> = 5.6 Hz, 2H), 3.73 (s, 3H), 3.45 (s, 3H)
4-237		4D	4-6	6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzo[d]thiazole-7-carbonitrile LCMS [M+1] ⁺ = 414.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 9.73 (s, 1H), 8.63 (d, <i>J</i> = 8.4 Hz, 1H), 8.45 (br s, 3H), 8.35 (s, 1H), 8.04 (d, <i>J</i> = 8.4 Hz, 1H), 7.92 (d, <i>J</i> = 8.4 Hz, 1H), 7.87 (s, 1H),

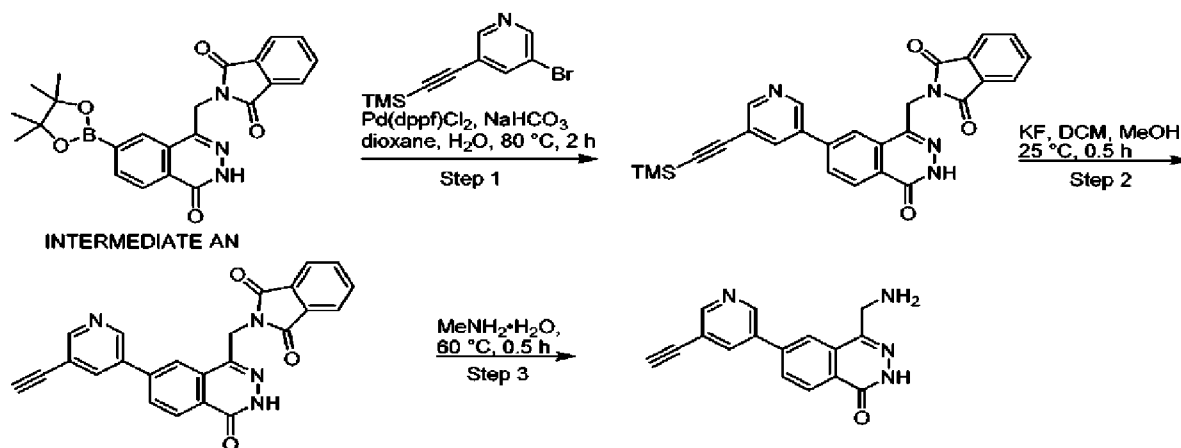
				7.36 (dd, $J = 1.2, 8.4$ Hz, 1H), 4.39 - 4.19 (m, 2H), 3.78 (s, 3H)
4-238		4B	4-13	4-(aminomethyl)-6-(5-(8-cyclopropoxyimidazo[1,5-a]pyridin-5-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS $[M+1]^+ = 428.0$; ^1H NMR (400MHz, DMSO- d_6) $\delta = 12.85$ (s, 1H), 8.48 (br s, 3H), 8.42 - 8.37 (m, 1H), 8.15 (br s, 1H), 8.05 - 7.99 (m, 1H), 7.87 (br s, 1H), 7.72 (br s, 1H), 7.40 (br d, $J = 8.4$ Hz, 1H), 7.26 - 7.19 (m, 1H), 6.85 - 6.78 (m, 1H), 4.42 - 4.31 (m, 1H), 4.29 - 4.17 (m, 2H), 3.81 - 3.79 (m, 2H), 3.81 - 3.79 (m, 1H), 2.15 - 2.07 (m, 1H), 0.99 - 0.79 (m, 4H)
4-239		4D	4-13	4-(aminomethyl)-6-(5-(imidazo[1,5-a]pyridin-8-yl)-1-methyl-1H-pyrazol-4-yl)phthalazin-1(2H)-one LCMS $[M+1]^+ = 372.1$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.83$ (s, 1H), 9.31 (s, 1H), 8.68 (d, $J = 7.2$ Hz, 1H), 8.50 (br s, 3H), 8.31 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 1.2$ Hz, 1H), 7.48 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.42 (s, 1H), 7.30 (d, $J = 6.8$ Hz, 1H), 7.15 (t, $J = 6.8$ Hz, 1H), 4.40 - 4.23 (m, 2H), 3.77 (s, 3H)
4-240		4F	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)indolizine-1-carbonitrile LCMS $[M+1]^+ = 396.1$; ^1H NMR (400 MHz, DMSO - d_6) $\delta = 12.84$ (s, 1H), 8.64 - 8.58 (m, 1H), 8.49 (br s, 3H), 8.27 (s, 1H), 8.11 - 8.05 (m, 2H), 7.97 (d, $J = 1.2$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.54 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.32 (ddd, $J = 1.2, 6.8, 9.2$ Hz, 1H), 7.04 (dt, $J = 1.2, 7.2$ Hz, 1H), 4.37 (br d, $J = 5.6$ Hz, 2H), 3.83 (s, 3H)
4-241		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-3-fluoro-4-methylbenzonitrile LCMS $[M+1]^+ = 445.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.87$ (s, 1H), 8.77 - 8.36 (m, 3H), 8.34 (s, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.76 (s, 1H), 7.74 (d, $J = 6.4$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 4.37 - 4.24 (m, 2H), 4.11 (td, $J = 2.8, 5.6$ Hz, 1H), 3.73 (s, 3H), 2.45 (s, 3H), 0.92 - 0.86 (m, 2H), 0.82 - 0.74 (m, 2H)

4-242		4D	4-8	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzo[b]thiophene-3-carbonitrile LCMS [M+] ⁺ = 413.1; ¹ H NMR (400 MHz, CD ₃ OD) δ (ppm) = 8.24 (d, <i>J</i> = 8.4 Hz, 1H), 8.15 (s, 1H), 8.13 - 8.09 (m, 1H), 8.02 - 7.98 (m, 1H), 7.78 - 7.75 (m, 1H), 7.72 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 7.70 - 7.61 (m, 2H), 3.98 (s, 3H), 3.83 (s, 2H)
4-243		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-(difluoromethoxy)benzonitrile LCMS [M] ⁺ = 457.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 12.89 (s, 1H), 8.55 (br s, 3H), 8.32 (s, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.90 - 7.88 (m, 1H), 7.88 - 7.85 (m, 1H), 7.83 - 7.79 (m, 1H), 7.79 - 7.52 (m, 1H), 7.47 - 7.42 (m, 1H), 4.39 - 4.27 (m, 2H), 3.81 - 3.74 (m, 3H)
4-244		4D	4-8	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)thieno[2,3-b]pyridine-3-carbonitrile LCMS [M+] ⁺ = 414.1; ¹ H NMR (400 MHz, CD ₃ OD) δ (ppm) = 8.79 (dd, <i>J</i> = 1.6, 4.8 Hz, 1H), 8.40 (dd, <i>J</i> = 1.6, 8.0 Hz, 1H), 8.26 (d, <i>J</i> = 8.4 Hz, 1H), 8.16 (s, 1H), 7.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.74 - 7.67 (m, 2H), 4.01 (s, 3H), 3.92 (s, 2H)
4-245		4G	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluoro-4-methyl-1-naphthonitrile LCMS [M+] ⁺ = 439.2; ¹ H NMR (400 MHz, CD ₃ OD) δ = 8.34 (d, <i>J</i> = 8.0 Hz, 1H), 8.23 (s, 1H), 8.18 (d, <i>J</i> = 8.4 Hz, 1H), 8.12 (d, <i>J</i> = 8.4 Hz, 1H), 7.90 - 7.83 (m, 2H), 7.83 - 7.76 (m, 1H), 7.49 - 7.37 (m, 1H), 4.52 - 4.29 (m, 2H), 3.85 (s, 3H), 2.79 (d, <i>J</i> = 2.4 Hz, 3H)
4-246		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-(difluoromethyl)-1-naphthonitrile LCMS [M+] ⁺ = 457.3; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.70 (br s, 1H), 8.89 (s, 1H), 8.49 - 8.41 (m, 2H), 8.25 (d, <i>J</i> = 8.1 Hz, 1H), 8.08 - 7.92 (m, 3H), 7.82 (s, 1H), 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.09 - 6.77 (m, 1H), 4.15 - 4.04 (m, 2H), 3.66 (s, 3H)

4-247		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-3-fluoro-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS [M + 1] ⁺ = 425.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.88 (s, 1H), 8.54 (d, <i>J</i> = 8.4 Hz, 1H), 8.46 (br s, 3H), 8.30 - 8.24 (m, 1H), 8.13 (d, <i>J</i> = 8.4 Hz, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.91 - 7.82 (m, 3H), 7.70 (s, 1H), 7.45 (dd, <i>J</i> = 1.2, 8.4 Hz, 1H), 4.25 (br d, <i>J</i> = 16.0 Hz, 1H), 4.06 (br d, <i>J</i> = 16.0 Hz, 1H), 3.71 (s, 3H)
4-248		4D	4-6	5-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-methyl-2H-indazole-4-carbonitrile LCMS [M+1] ⁺ = 411.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.80 (s, 1H), 8.49 (br s, 3H), 8.33 (s, 1H), 8.19 (dd, <i>J</i> = 0.8, 8.8 Hz, 1H), 8.02 (d, <i>J</i> = 8.4 Hz, 1H), 7.86 (d, <i>J</i> = 1.2 Hz, 1H), 7.49 (d, <i>J</i> = 8.8 Hz, 1H), 7.36 (dd, <i>J</i> = 2.4, 8.4 Hz, 1H), 4.33 - 4.19 (m, 5H), 3.75 (s, 3H)
4-249		4D	4-6	5-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-methyl-1H-indazole-4-carbonitrile LCMS [M+1] ⁺ = 411.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.48 - 8.37 (m, 3H), 8.36 - 8.26 (m, 3H), 8.02 (d, <i>J</i> = 8.4 Hz, 1H), 7.83 (s, 1H), 7.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.34 (br d, <i>J</i> = 8.4 Hz, 1H), 4.22 (m, 5H), 3.74 (s, 3H)
4-250		4D	4-6	5-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzo[c]isothiazole-4-carbonitrile LCMS [M+1] ⁺ = 414.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.87 (s, 1H), 10.07 (d, <i>J</i> = 1.2 Hz, 1H), 8.39 - 8.25 (m, 5H), 8.07 (d, <i>J</i> = 8.4 Hz, 1H), 7.88 (s, 1H), 7.77 (d, <i>J</i> = 9.2 Hz, 1H), 7.45 (dd, <i>J</i> = 1.6, 8.4 Hz, 1H), 4.37 - 4.23 (m, 2H), 3.84 - 3.80 (m, 3H)
4-251		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-3-fluorobenzonitrile LCMS [M+1] ⁺ = 431.1; ¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ= 12.88 (s, 1 H), 8.45 (s, 3 H), 8.35 (s, 1 H), 8.14 (d, <i>J</i> =8.4 Hz, 1 H), 7.86 - 7.93 (m, 1 H), 7.77 - 7.83 (m, 2 H), 7.47 (d, <i>J</i> =8.4, 1.10 Hz, 1 H), 4.25 - 4.39 (m, 2 H), 4.12 - 4.20 (m, 1 H),

				3.75 (s, 3 H), 0.85 - 0.93 (m, 2 H), 0.75 - 0.84 (m, 2 H)
4-252		4D	4-6	2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-(trifluoromethoxy)benzonitrile LCMS [M+]⁺ = 497.1; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 8.51 (br s, 3H), 8.30 (s, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.80 (s, 1H), 7.68 (d, <i>J</i> = 1.2 Hz, 1H), 7.46 - 7.39 (m, 2H), 4.32 (br d, <i>J</i> = 5.6 Hz, 2H), 4.28 - 4.21 (m, 1H), 3.76 (s, 3H), 0.96 - 0.77 (m, 4H)

EXAMPLE 4-253



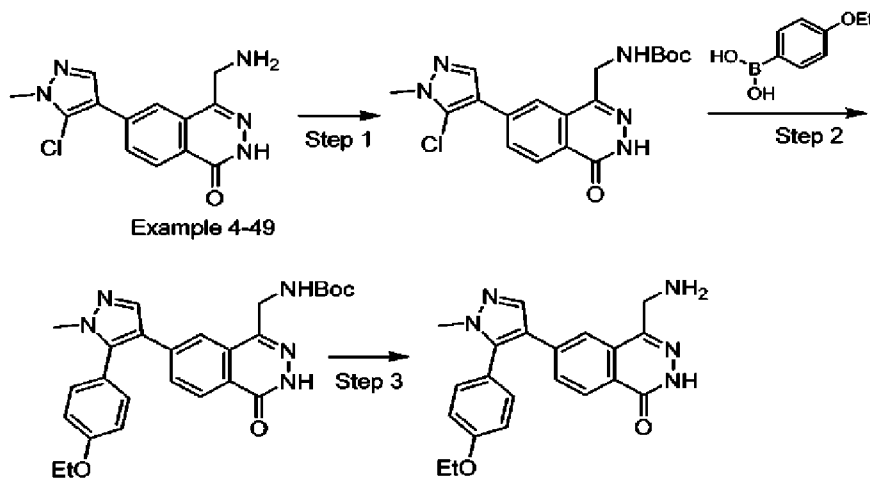
[0474] **Step 1:** To a solution of Intermediate AN (136 mg, 315 μ mol, 1.00 *eq.*) in dioxane (4 mL) and water (0.80 mL) was added Pd(dppf)Cl₂ (23 mg, 32 μ mol, 0.10 *eq.*) and sodium bicarbonate (79 mg, 944 μ mol, 37 μ L, 3.00 *eq.*) and the reaction mixture was stirred at 80 °C for 2 hours. After such time the reaction was filtered, the filtrate was concentrated in vacuum to a residue, the residue was purified by prep-TLC (petroleum ether : ethyl acetate 10-100%) to give 2-[[4-oxo-7-[5-(2-trimethylsilylethynyl)-3-pyridyl]-3H-phthalazin-1-yl]methyl]isoindoline-1,3-dione (100 mg, 209 μ mol, 66% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.32 (s, 1H), 8.96 (d, *J* = 2.4 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.36 - 8.31 (m, 2H), 8.14 (s, 2H), 7.79 - 7.74 (m, 2H), 7.73 - 7.69 (m, 2H), 5.19 (s, 2H), 0.09 (s, 9H).

[0475] **Step 2:** To a solution of 2-[[4-oxo-7-[5-(2-trimethylsilylethynyl)-3-pyridyl]-3H-phthalazin-1-yl]methyl]isoindoline-1,3-dione (100 mg, 209 μ mol, 1.00 *eq.*) in methanol (2 mL) and dichloromethane (2 mL) was added potassium fluoride (36 mg, 627 μ mol, 14.7 μ L,

3.00 *eq.*), and the reaction was stirred at 25 °C for 0.5 hour. The reaction was concentrated under vacuum and the residue was triturated with water (5 mL), filtered and the filter cake was dried in vacuum to give 2-[[7-(5-ethynyl-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (80 mg, 197 μmol, 94% yield) as a brown solid. LCMS $[M+1]^+ = 407.0$.

[0476] **Step 3:** A mixture of 2-[[7-(5-ethynyl-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (80 mg, 197 μmol, 1.00 *eq.*) in methylamine aqueous solution (4 mL) was stirred at 60 °C for 0.5 hour. After such time the reaction was concentrated under vacuum and the residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150 × 25 × 10 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-25%, 10 min) and lyophilization to give 4-(aminomethyl)-6-(5-ethynyl-3-pyridyl)-2*H*-phthalazin-1-one, example 4-253 (10 mg, 32.1 μmol, 16% yield) as a yellow solid. LCMS $[M+1]^+ = 277.2$. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.01 (s, 1H), 9.17 (d, *J* = 2.4 Hz, 1H), 8.81 (d, *J* = 1.6 Hz, 1H), 8.60 - 8.49 (m, 4H), 8.41 - 8.37 (m, 1H), 8.36 - 8.30 (m, 2H), 4.65 - 4.55 (m, 3H).

EXAMPLE 4-254



[0477] **Step 1:** A mixture of 4-(aminomethyl)-6-(5-chloro-1-methyl-pyrazol-4-yl)-2*H*-phthalazin-1-one, Example 4-49 (45 mg, 155 μmol, 1.00 *eq.*), di-*tert*-butyl dicarbonate (68 mg, 311 μmol, 71 μL, 2.00 *eq.*) and triethylamine (47 mg, 466 μmol, 65 μL, 3.00 *eq.*) in dichloromethane (1.00 mL) was purged with nitrogen 3 times and stirred at 25 °C for 3 hours. After such time the mixture was concentrated under reduced pressure to a residue. The mixture was triturated with petroleum ether (3 mL) and filtered to give *tert*-butyl *N*-[[7-(5-chloro-1-methyl-pyrazol-4-yl)-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (40 mg, 96 μmol,

62% yield) as a yellow solid. LCMS $[M+1]^+ = 390.2$. ^1H NMR (400 MHz, MeOD) $\delta = 8.41$ (d, $J = 8.4$ Hz, 1H), 8.33 (s, 1H), 8.19 (br d, $J = 8.4$ Hz, 1H), 8.05 (s, 1H), 4.62 (s, 2H), 3.96 - 3.92 (s, 3H), 1.48 - 1.40 (s, 9H).

[0478] **Step 2:** A mixture of (4-ethoxyphenyl)boronic acid (16 mg, 98.5 μmol , 1.20 *eq.*), *tert*-butyl *N*-[[7-(5-chloro-1-methyl-pyrazol-4-yl)-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (32 mg, 82 μmol , 1.00 *eq.*), sodium carbonate (26 mg, 246 μmol , 3.00 *eq.*) and Pd(dppf)Cl₂ (6 mg, 8 μmol , 0.10 *eq.*) in dioxane (3 mL) and water (0.6 mL) was purged with nitrogen 3 times and stirred at 110 °C for 12 hours. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate 10-100%) to give *tert*-butyl-*N*-[[7-[5-(4-ethoxyphenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (28 mg, 45 μmol , 54% yield) as a white solid. LCMS $[M+1]^+ = 476.2$.

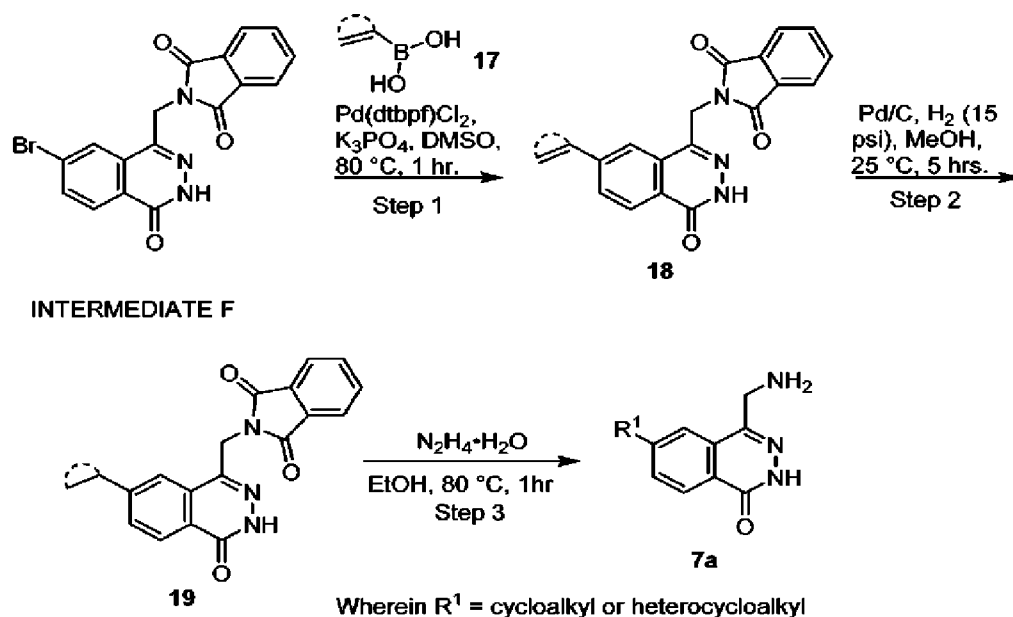
[0479] **Step 3:** A mixture of *tert*-butyl-*N*-[[7-[5-(4-ethoxyphenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (28 mg, 59 μmol , 1.00 *eq.*) and trifluoroacetic acid (1.08 g, 9.45 mmol, 700 μL , 161 *eq.*), in dichloromethane (3 mL) was purged with nitrogen 3 times and stirred at 25 °C for 1 hour. After such time the mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (Phenomenex Gemini-NX C18 75 $\times$ 30 mm $\times$ 3 μm ; mobile phase: [water (0.1% TFA)-ACN]; B%: 20%-30%, 7 min) to give 4-(aminomethyl)-6-[5-(4-ethoxyphenyl)-1-methyl-pyrazol-4-yl]-2*H*-phthalazin-1-one, Example 4-254 (25 mg, 49 μmol , 83% yield, TFA salt) as an off-white solid. LCMS $[M+1]^+ = 376.1$. ^1H NMR (400 MHz, DMSO-*d*₆) $\delta = 12.84$ (s, 1H), 8.34 (br s, 3H), 8.12 (s, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 1.2$ Hz, 1H), 7.51 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 4.31 (br d, $J = 4.4$ Hz, 2H), 4.11 (q, $J = 6.8$ Hz, 2H), 3.72 (s, 3H), 1.37 (t, $J = 6.8$ Hz, 3H).

EXAMPLES 5-1 and 5-2

GENERAL COUPLING METHOD FOR THE PREPARATION OF

EXAMPLES 5-1 AND 5-2

Coupling Method 5:



[0480] **Step 1:** A mixture of Intermediate F (200 mg, 521 μ mol, 1.00 *eq.*), R^1 -boronic acid 17 where R^1 is cycloalkenyl or heterocycloalkenyl (781 μ mol, 1.50 *eq.*), di-*tert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (34 mg, 52 μ mol, 0.10 *eq.*), potassium phosphate (221 mg, 1.04 mmol, 2.00 *eq.*) in dimethylsulfoxide (2.5 mL) was purged with nitrogen 3 times and the mixture stirred at 80 °C for 1 hour and cooled to room temperature. Water (50 mL) was then added and the mixture extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo and the residue purified by column chromatography (SiO_2 , dichloromethane/methanol 0 to 10% methanol) to give the corresponding coupled product 18 as a light-yellow solid.

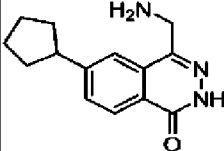
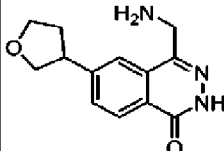
[0481] **Step 2:** To a solution of the corresponding coupled product 18 (296 μ mol, 1.00 *eq.*) in methanol (6 mL) was added 10% palladium on activated carbon (10 mg). The mixture was purged with hydrogen several times and stirred under a hydrogen atmosphere (15 psi) at 25 °C for 5 hours. After such time the reaction mixture was filtered and concentrated to give the

corresponding reduced product **19** as a white solid which was used in the next step without further purification.

[0482] **Step 3:** A mixture of the corresponding reduced product **19** and hydrazine hydrate (27 mg, 536 μ mol, 26 μ L) in ethanol (5 mL) was stirred at 80 °C for 1 hour. The reaction mixture was evaporated and the residue was purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 16%-36%, 9 min) to give the desired R¹ amino compounds where R¹ is cycloalkyl or heterocycloalkyl.

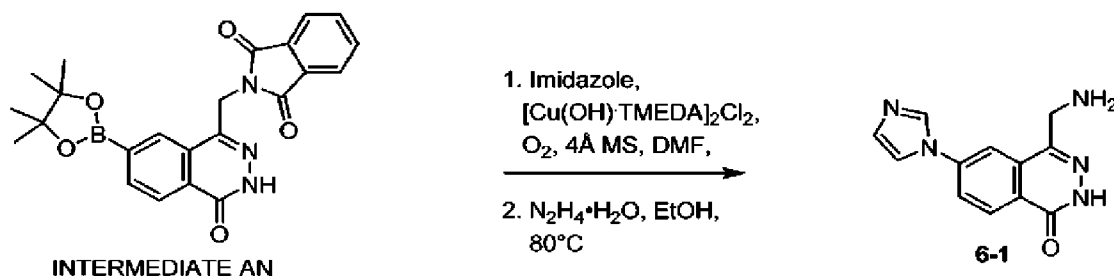
[0483] Following the teachings of the General Reaction Schemes, the coupling method 5 and the Intermediates disclosed herein, the Examples **5-1** to **5-2** are prepared as shown in Table 5:

Table 5

Example	Structure	Compound Name and Characterization
5-1		4-(aminomethyl)-6-cyclopentylphthalazin-1(2H)-one; LCMS [M+] ⁺ 244.2; ¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.43 (br s, 3H), 8.22 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 4.47 (br d, J = 4.8 Hz, 2H), 3.27 - 3.16 (m, 1H), 2.18 - 2.05 (m, 2H), 1.84 (m, 2H), 1.77 - 1.61 (m, 4H).
5-2		(R,S)-4-(aminomethyl)-6-(THF-3-yl)phthalazin-1(2H)-one; LCMS [M+] ⁺ 246.1; ¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.53 (s, 3H), 8.24 (d, J = 8.8 Hz, 1H), 7.89 - 7.81 (m, 2H), 4.46 (br d, J = 5.2 Hz, 2H), 4.14 - 3.98 (m, 2H), 3.85 (q, J = 7.6 Hz, 1H), 3.75 - 3.58 (m, 2H), 3.44 - 3.36 (m, 1H), 2.11-2.02 (m, 1H).

PREPARATION of EXAMPLES 6-1 to 6-5

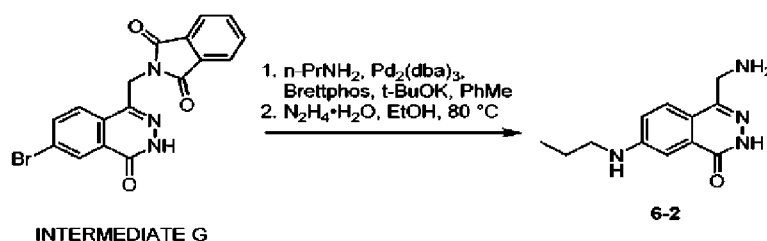
EXAMPLE 6-1



[0484] **Step 1:** A mixture of Intermediate AN (86 mg, 200 μ mol, 1.00 eq.), imidazole (68 mg, 1.00 mmol, 5.00 eq.), chloro(hydroxy)copper-N,N,N',N'-tetramethylethane-1,2-diamine (9 mg, 20 μ mol, 0.10 eq.) and 4Å molecular sieve (10 mg) in DMF (5 mL) was degassed and purged with oxygen 3 times. The mixture was then stirred at 25 °C for 12 hours under an oxygen atmosphere (15 psi). After such time the mixture was filtered and concentrated under reduced pressure and the residue purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.225% FA)-ACN]; B%: 3%-33%, 10 min) to give 2-[(7-imidazol-1-yl-4-oxo-3H-phthalazin-1-yl)methyl]isoindoline-1,3-dione (4 mg, 10.8 μ mol, 5% yield) as a white solid LCMS $[M+1]^+ = 372.1$.

[0485] **Step 2:** To a solution of 2-[(7-imidazol-1-yl-4-oxo-3H-phthalazin-1-yl)methyl]isoindoline-1,3-dione (3 mg, 8 μ mol, 1.00 eq.) in ethyl alcohol (1.00 mL) was added hydrazine hydrate (4 mg, 81 μ mol, 3 μ L, 10.0 eq.). The mixture was stirred at 80 °C for 1 hour and then the mixture was concentrated under reduced pressure. The concentrated residue was then purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-20%, 9 min) to give 4-(aminomethyl)-6-imidazol-1-yl-2H-phthalazin-1-one, example 6-1 (1.4 mg, 5 μ mol, 61% yield) as an off-white solid. LCMS $[M+1]^+ = 242.1$. ^1H NMR (400 MHz, DMSO- d_6) δ = 13.12 (s, 1H), 9.71 - 9.57 (s, 1H), 8.70 - 8.61 (brs, 3H), 8.49 (d, J = 8.8 Hz 1H), 8.47 (s, 1H), 8.44 (s, 1H), 8.33 (dd, J = 2.0, 8.8 Hz, 1H), 7.77 (br s, 1H), 4.53 (br d, J = 5.6 Hz, 2H).

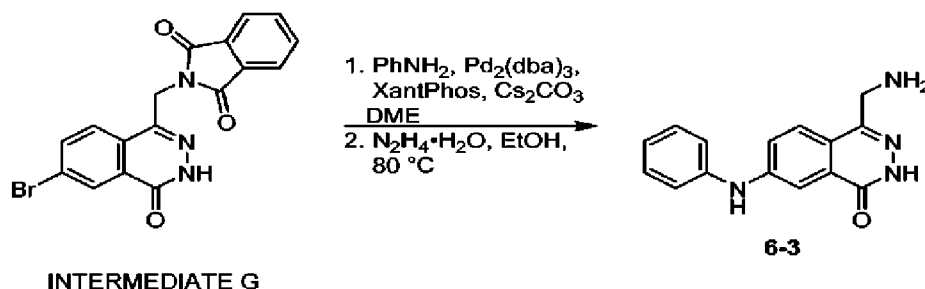
EXAMPLE 6-2



[0486] **Step 1:** To a solution of Intermediate G (50 mg, 130 μ mol, 1.00 eq.) and propan-1-amine (9 mg, 156 μ mol, 13 μ L, 1.20 eq.) in toluene (2 mL) was added $\text{Pd}_2(\text{dba})_3$ (24 mg, 26 μ mol, 0.20 eq.), potassium *tert*-butoxide (29 mg, 260 μ mol, 2.00 eq.) and BrettPhos (140 mg, 260 μ mol, 2.00 eq.) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 12 hours. After such time the mixture was concentrated in vacuo and the residue dissolved in a water: methyl alcohol 2: 1 mixture (3 mL) and filtered. The filtrate was concentrated in vacuo

to give 2-[[4-oxo-6-(propylamino)-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (35 mg, crude) as a yellow solid, which was used in the next step without further purification. LCMS $[M+1]^+ = 381.1$.

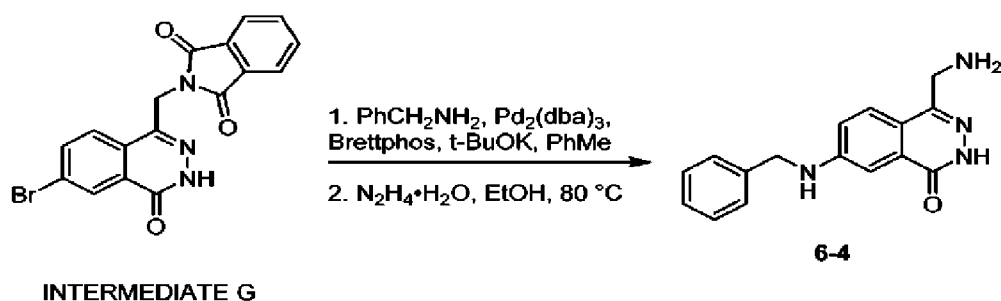
EXAMPLE 6-3



[0487] **Step 1** To a solution of Intermediate G (200 mg, 521 μmol , 1.00 *eq.*) and aniline (58 mg, 624 μmol , 57.0 μL , 1.20 *eq.*) in DME (3 mL) was added cesium carbonate (678 mg, 2.08 mmol, 4.00 *eq.*), $\text{Pd}_2(\text{dba})_3$ (48 mg, 52 μmol , 0.10 *eq.*) and Xantphos (331 mg, 572 μmol , 1.10 *eq.*). The mixture was stirred at 95 °C for 12 hours under nitrogen atmosphere. After such time the mixture was concentrated in vacuo and the residue taken up in water (5 mL) and methyl alcohol (5 mL) then filtered. The filtrate was concentrated in vacuum to give 2-[(6-anilino-4-oxo-3*H*-phthalazin-1-yl)methylcarbamoyl]benzoic acid (200 mg, crude) as a yellow solid, which was used in the next step without further purification.

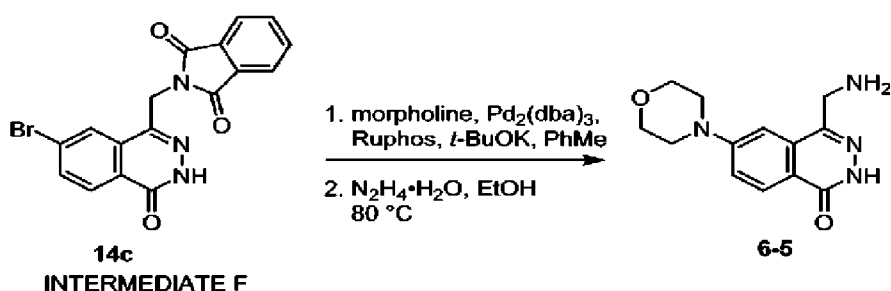
[0488] **Step 2:** To a solution of 2-[(6-anilino-4-oxo-3*H*-phthalazin-1-yl)methylcarbamoyl]benzoic acid (50 mg, crude) in ethyl alcohol (1 mL) was added hydrazine hydrate (12.9 mg, 252 μmol , 12.5 μL). The mixture was stirred at 80 °C for 12 hours. After such time the mixture was concentrated in vacuo and the residue purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 2%-32%, 10 min) to give 4-(aminomethyl)-7-anilino-2*H*-phthalazin-1-one, example 6-3 (10 mg, 33 μmol , 24% yield) as a yellow solid. LCMS $[M+1]^+ = 267.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 12.63 (s, 1H), 9.17 (s, 1H), 8.43 (br s, 3H), 7.82 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 2.4, 8.8 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.28 - 7.23 (m, 2H), 7.07 (t, J = 7.2 Hz, 1H), 4.37 (br s, 2H).

EXAMPLE 6-4



[0489] **Step 1:** To a solution of Intermediate G (50 mg, 130 μ mol, 1.00 *eq.*) and phenylmethanamine (17 mg, 156 μ mol, 17.0 μ L, 1.20 *eq.*) in toluene (2 mL) was added $\text{Pd}_2(\text{dba})_3$ (24 mg, 26 μ mol, 0.20 *eq.*), potassium *tert*-butoxide (29 mg, 260 μ mol, 2.00 *eq.*) and BrettPhos (140 mg, 260 μ mol, 2.00 *eq.*) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 12 hours. After such time the mixture was concentrated in vacuo and the residue dissolved in a water: methyl alcohol 2:1 mixture (3 mL) and filtered. The filtrate was concentrated in vacuo to give 2-[[6-(benzylamino)-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (35 mg, crude) as a yellow solid, which was used directly in the next step without further purification. LCMS $[\text{M}+1]^+ = 429.1$. To a solution of 2-[[6-(benzylamino)-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl] benzoic acid (35 mg, crude) in ethyl alcohol (1 mL) was added hydrazine hydrate (9 mg, 171 μ mol, 8 μ L). The mixture was stirred at 80 °C for 12 hours. After such time the mixture was concentrated in vacuo and the residue purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 2%-32%, 10 min) to give 4-(aminomethyl)-7-(benzylamino)-2*H*-phthalazin-1-one, example 6-4 (7 mg, 22 μ mol, 17% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 281.2$. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.49 (s, 1H), 8.32 (br s, 3H), 7.67 (d, *J*=8.8 Hz, 1H), 7.58 - 7.50 (m, 1H), 7.37 - 7.32 (m, 4H), 7.27 - 7.19 (m, 3H), 4.45 (br s, 2H), 4.31 (br d, *J*=6.0 Hz, 2H).

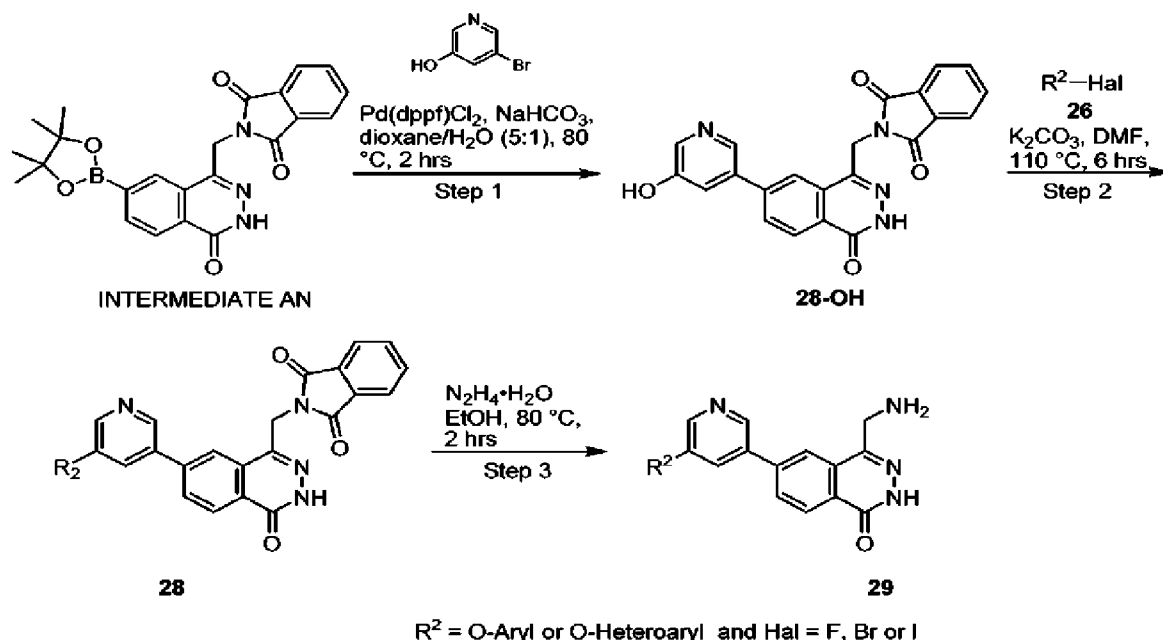
EXAMPLE 6-5



[0490] **Step 1:** To a solution of Intermediate F (50 mg, 130 μmol , 1.00 *eq.*) and morpholine (17 mg, 195 μmol , 17 μL , 1.50 *eq.*) in toluene (2 mL) was added $\text{Pd}_2(\text{dba})_3$ (12 mg, 13 μmol , 0.10 *eq.*), potassium *tert*-butoxide (44 mg, 390 μmol , 3.00 *eq.*) and RuPhos (121 mg, 260 μmol , 2.00 *eq.*) under a nitrogen atmosphere. The mixture was stirred at 100 $^\circ\text{C}$ for 2 hours. After such time the mixture was concentrated in vacuo and the residue dissolved in a water:methyl alcohol 2:1 mixture (3 mL) and filtered. The filtrate was concentrated in vacuo to give 2-(morpholine-4-carbonyl)-*N*-[(7-morpholino-4-oxo-3*H*-phthalazin-1-yl)methyl]benzamide (35.0 mg, crude) as a yellow solid which was used directly in the next step without further purification. LCMS $[\text{M}+1]^+ = 478.2$. To a solution of 2-(morpholine-4-carbonyl)-*N*-[(7-morpholino-4-oxo-3*H*-phthalazin-1-yl)methyl]benzamide (35 mg, crude) in ethyl alcohol (1 mL) was added hydrazine hydrate (9 mg, 176 μmol , 9 μL). The mixture was stirred at 80 $^\circ\text{C}$ for 12 hours. After such time the mixture was concentrated in vacuo and the residue purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 25 $\times$ 10 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 3%-23%, 9 min) to give 4-(aminomethyl)-6-morpholino-2*H*-phthalazin-1-one, example 6-5 (9 mg, 28 μmol , 32% yield) as a white solid. LCMS $[\text{M}+1] = 261.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 12.56 (s, 1H), 8.50 (br s, 3H), 8.08 (d, J = 9.2 Hz, 1H), 7.51 (dd, J = 2.4, 9.2 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 4.38 (q, J = 5.6 Hz, 2H), 3.79 - 3.76 (m, 4H), 3.47 - 3.41 (m, 4H).

GENERAL COUPLING METHOD AND PURIFICATION METHODS FOR THE
PREPARATION OF EXAMPLES 7-1 to 7-6

GENERAL METHOD 7



[0491] **Step 1:** A mixture of Intermediate AN (150 mg, 348 μmol , 1.00 *eq.*), 5-bromopyridin-3-ol (522 μmol , 1.5 *eq.*), Pd(dppf)Cl_2 (26 mg, 35 μmol , 0.10 *eq.*), sodium bicarbonate (58 mg, 696 μmol , 27 μL , 2.00 *eq.*) in dioxane (1 mL) and water (0.2 mL) was degassed and purged with nitrogen 3 times. The mixture was stirred at 80°C for 3 hours under a nitrogen atmosphere. Upon completion the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The aqueous phase was filtered, and the filter cake dried to give the corresponding R^2 -Pyridyl-Suzuki coupling product **28-OH** which was used directly in the next step without further purification.

[0492] **Step 2:** To a solution of Pyridyl-Suzuki coupling product **28-OH** (80 mg, crude) in DMF (1 mL) was added potassium carbonate (83 mg, 602 μmol) and aryl/heteroaryl-substituted fluoride/bromide **26** (54 mg, 402 μmol). The mixture was stirred at 120°C for 6 hours to furnish R^2 -Pyridyl- $\text{S}_{\text{N}}\text{Ar}$ coupling product **28**. The reaction mixture was used in the next step directly without further purification.

[0493] **Step 3:** To a solution of corresponding R^2 -Pyridyl- $\text{S}_{\text{N}}\text{Ar}$ coupling product **28** (50 mg, crude) in ethyl alcohol (10 mL) was added hydrazine hydrate (11.0 mg, 210 μmol , 10 μL).

The mixture was stirred at 80 °C for 2 hours and the cooled mixture was concentrated in vacuo. The concentrated residue **29** was purified by prep-HPLC according to one of the purification methods 7-1 through 7-3 to return desired compounds shown in table 7.

[0494] **Purification Methods (PM)**

[0495] **PM 7-1:** column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 5%-25%, 11 min.

[0496] **PM 7-2:** column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 2%-32%, 10 min,

[0497] **PM 7-3:** column: Shim-pack C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1 % TFA)-ACN]; B%: 1%-20%, 10 min.

[0498] Following the teachings of the General Reaction Schemes, coupling method 7 and using purification methods 7-1 through 7-3 and the Intermediates disclosed herein, the Examples 7-1 to 7-6 are prepared as shown in Table 7.

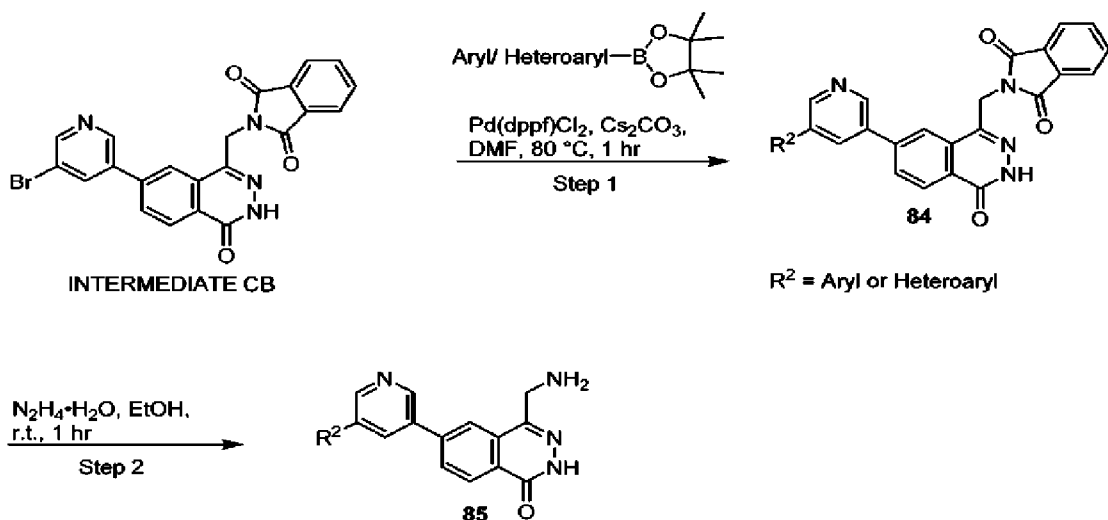
Table 7

Examples	Structure	PM	Compound Name and Characterization
7-1		7-3	4-(aminomethyl)-6-(5-(pyridin-4-yloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 346.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.02 (s, 1H), 9.17 (s, 1H), 8.69 (s, 1H), 8.63 (br d, J = 5.2 Hz, 2H), 8.46 - 8.37 (m, 5H), 8.36 (s, 1H), 8.33 (s, 1H), 7.25 (br s, 2H), 4.59 (br d, J = 5.6 Hz, 2H).
7-2		7-2	2-((5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)oxy)benzonitrile LCMS [M+1] ⁺ = 370.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.99 (s, 1H), 8.55 (d, J = 2.8 Hz, 1H), 8.41 - 8.36 (m, 2H), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 4.13 (s, 2H).
7-3		7-1	4-(aminomethyl)-6-(5-(4-fluorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 363.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.00 (s, 1H), 9.02 (d, J = 1.6 Hz, 1H), 8.66 - 8.51 (brs, 3H), 8.47 (d, J = 2.8 Hz, 1H), 8.40 - 8.25 (m, 3H), 8.17 (s, 1H), 7.33 - 7.21 (m, 4H), 4.57 (br d, J = 5.6 Hz, 2H).

7-4		7-1	4-(aminomethyl)-6-(5-(4-chlorophenoxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 379.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.00 (s, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.60 (br s, 3H), 8.53 (d, J = 2.4 Hz, 1H), 8.40 - 8.35 (d, J = 8.0 Hz, 1H), 8.34 - 8.27 (m, 2H), 8.22 (t, J = 2.4 Hz, 1H), 7.54 - 7.45 (d, J = 8.8 Hz, 2H), 7.22 - 7.15 (d, J = 8.8 Hz, 2H), 4.63 - 4.53 (d, J = 5.6 Hz, 2H).
7-5		7-2	4-(aminomethyl)-6-(5-(p-tolyloxy)pyridin-3-yl)phthalazin-1(2H)-one LCMS [M+1] ⁺ = 359.3; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.82 (d, J = 1.6 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.37 - 8.32 (m, 2H), 8.14 - 8.09 (m, 1H), 7.87 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 2.33 (s, 3H).
7-6		7-2	4-((5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)oxy)benzonitrile LCMS [M+1] ⁺ = 370.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.98 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 2.8 Hz, 1H), 8.39 - 8.34 (m, 2H), 8.18 (dd, J = 2.0, 8.4 Hz, 1H), 8.11 (t, J = 2.4 Hz, 1H), 7.90 - 7.83 (dd, J = 2.0, 7.2 Hz, 2H), 7.31 - 7.25 (dd, J = 2.4, 6.8 Hz, 2H), 4.12 (s, 2H).

COUPLING METHODS (CM) AND PURIFICATION METHODS FOR THE PREPARATION OF EXAMPLES 8-1 to 8-9

CM 8A

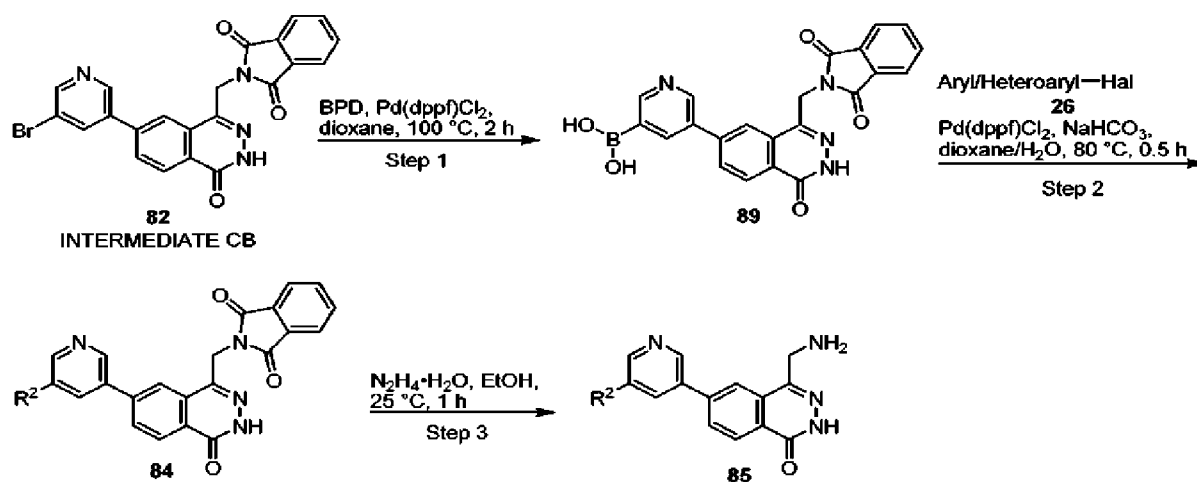


[0499] **Step 1:** A mixture of Intermediate CB (100 mg, 217 μmol, 1.00 *eq.*), an appropriate aryl/heteroaryl boronic ester (260 μmol, 1.20 *eq.*), cesium carbonate (141 mg, 434 μmol, 2.00 *eq.*) and Pd(dppf)Cl₂ (16.0 mg, 22 μmol, 0.10 *eq.*) in dimethylformamide (2 mL) was purged with nitrogen 3 times and stirred at 80 °C for 1 hour. Upon completion, the reaction mixture

was poured into water (50 mL), filtered and filter cake dried under reduced pressure to give the appropriate R²-pyridyl coupled product **84** (113 mg, crude) as a yellow solid that was used in the next step without further purification.

[0500] **Step 2:** To a solution of **84** (63 mg, crude) in ethyl alcohol (10 mL) was added hydrazine hydrate (13 mg, 251 μ mol, 12 μ L). The mixture was stirred at 35 °C for 1 hour and upon completion the mixture was adjusted pH to 1 with hydrochloric acid (1 M, 1 mL) and concentrated under reduced pressure. The residue was diluted with hydrochloric acid (1 M, 40.0 mL) and washed with ethyl acetate (30 mL $\times$ 3) and the aqueous phase was concentrated under reduced pressure. The residue was purified by prep-HPLC according to one of the purification methods 8-1 or 8-2 to give desired compounds **85**.

CM 8B



[0501] **Step 1:** A mixture of Intermediate CB (300 mg, 650 μ mol, 1.00 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (BPD) (198 mg, 780 μ mol, 1.20 eq), Pd(dppf)Cl₂ (47 mg, 65 μ mol, 0.10 eq) and potassium acetate (128 mg, 1.30 mmol, 2.00 eq) in dioxane (5 mL) was degassed and purged with nitrogen 3 times, and stirred at 100 °C for 2 hours under a nitrogen atmosphere to furnish [5-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2H-phthalazin-6-yl]-3-pyridyl]boronic acid **89**. The reaction mixture was used directly in next step. LCMS [M+1]⁺ = 427.2.

[0502] **Step 2:** A mixture of [5-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2H-phthalazin-6-yl]-3-pyridyl]boronic acid **89** (130 mg, 305 μ mol, 1.00 eq), an appropriate R² bromide **42** (610 μ mol, 2.00 eq), Pd(dppf)Cl₂ (22 mg, 31 μ mol, 0.10 eq), sodium bicarbonate (51 mg, 610

μmol , 24 μL , 2.00 eq) in dioxane (4 mL) and water (0.8 mL) was degassed and purged with nitrogen 3 times, stirred at 80 °C for 0.5 hour under a nitrogen atmosphere. Upon completion the reaction mixture was concentrated under reduced pressure to give a residue that was purified by column chromatography (SiO_2 , petroleum ether/ ethyl acetate 10:1 to 0:1, then dichloromethane/ methanol 10/ 1) to give R^2 -pyridyl coupled product **84** (150 mg, crude) as a black solid.

[0503] **Step 3:** To a solution of R^2 -pyridyl coupled product **84** (109 mg, 215 μmol , 1.00 eq) in ethyl alcohol (3.0 mL) was added hydrazine hydrate (110 mg, 2.15 mmol, 106 μL , 10.0 eq). The reaction mixture was stirred at 25 °C for 1 hour. Upon completion the reaction mixture was concentrated under reduced pressure to give a residue. The residue was acidified to pH 3 with hydrochloric acid (1M, 2 mL) and extracted with ethyl acetate (2 mL $\times$ 3). The aqueous phase was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC according to one of the purification methods 8-1 or 8-2 to give desired compounds **85** as off-white solids.

Purification methods

[0504] **PM 8-1:** column: Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 10%-35%, 6.5 min.

[0505] **PM 8-2:** column: Phenomenex Luna C18 150 $\times$ 25 mm $\times$ 10 μm ; mobile phase: [water (0.1% TFA)-ACN]; B%: 10%-40%, 10 min.

[0506] Following the teachings of the General Reaction Schemes, the coupling methods 8A and 8B and using purification methods 8-1 and 8-2 and the Intermediates disclosed herein, the Examples **8-1** to **8-9** are prepared as shown in Table 8.

Table 8

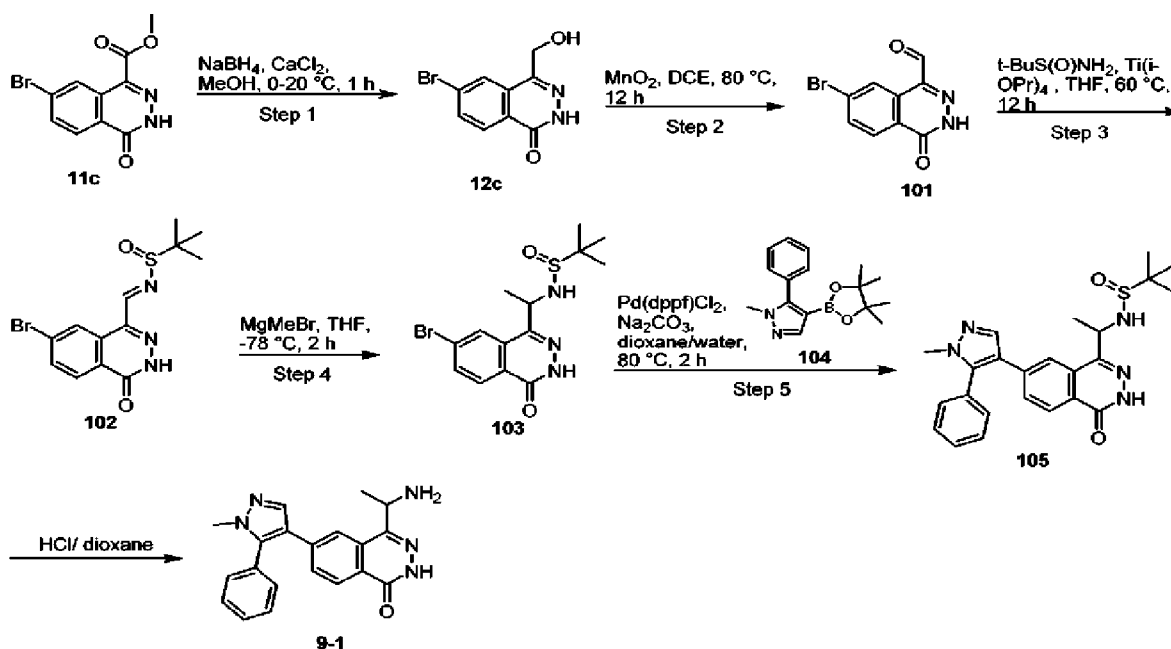
Example #	Structure	CM	PM	Compound Name and Characterization
8-1		8A	8-1	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-4-fluorobenzonitrile; LCMS $[\text{M}+1]^+ = 372.2$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta =$ 13.01 (s, 1H), 9.33 (d, $J = 2.0$ Hz, 1H), 8.97 (d, $J = 2.0$ Hz, 1H), 8.68 (t, $J = 2.0$ Hz, 1H), 8.59 (br s, 3H), 8.42 (m, 3H), 8.18 (dd, $J = 5.6, 8.8$ Hz, 1H), 7.88 (dd, $J = 2.8, 9.6$ Hz, 1H), 7.60 (dt, $J = 2.8, 8.4$ Hz, 1H), 4.59 (br d, $J = 5.6$ Hz, 2H).

8-2		8B	8-1	4-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)isophthalonitrile LCMS [M+1] ⁺ = 379.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.02 (s, 1H), 9.33 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.72 (d, J = 1.6 Hz, 1H), 8.67 (t, J = 2.0 Hz, 1H), 8.52 (br s, 3H), 8.45 - 8.41 (d, J = 8.4 Hz, 1H), 8.40 (s, 2H), 8.37 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 4.59 (s, 2H)
8-3		8A	8-3	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-5-methoxybenzonitrile; LCMS [M+1] ⁺ = 384.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.53 (t, J = 2.0 Hz, 1H), 8.47 - 8.41 (m, 2H), 8.41 - 8.36 (s, 3H), 8.36 - 8.34 (m, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 2.8 Hz, 1H), 7.47 (dd, J = 2.8, 8.8 Hz, 1H), 4.61 (br d, J = 2.8 Hz, 2H), 3.90 (s, 3H)
8-4		8B	8-1	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-5-chlorobenzonitrile; LCMS [M+1] ⁺ = 388.0; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.33 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 2.0 Hz, 1H), 8.68 (t, J = 2.0 Hz, 1H), 8.60 (br s, 3H), 8.44 - 8.37 (m, 3H), 8.29 (d, J = 2.0 Hz, 1H), 8.03 - 7.98 (dd, J = 8.4, 2.4 Hz, 1H), 7.94 - 7.89 (d, J = 8.4 Hz, 1H), 4.66 - 4.49 (d, J = 5.6 Hz, 2H)
8-5		8A	8-1	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-5-fluorobenzonitrile; LCMS [M+1] ⁺ = 372.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.32 (d, J = 2.0 Hz, 1H), 8.94 (d, J = 2.0 Hz, 1H), 8.68 (t, J = 2.0 Hz, 1H), 8.61 (br s, 3H), 8.44 - 8.37 (m, 3H), 8.11 (dd, J = 2.8, 8.8 Hz, 1H), 7.95 (dd, J = 5.6, 8.8 Hz, 1H), 7.82 (dt, J = 2.8, 8.8 Hz, 1H), 4.58 (br d, J = 5.6 Hz, 2H)
8-6		8B	8-3	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-4-chlorobenzonitrile; LCMS [M+1] ⁺ = 388.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.33 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.67 (t, J = 2.0 Hz, 1H), 8.58 (br s, 3H), 8.42 (m, 3H), 8.12 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 2.0, 8.4 Hz, 1H), 4.59 (br d, J = 5.6 Hz, 2H)
8-7		8A	8-3	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-4-methylbenzonitrile; LCMS [M+1] ⁺ = 368.1; ¹ H NMR (400 MHz, MeOD) δ = 9.11 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.62 - 8.52 (m, 2H), 8.34 (dd, J = 1.2, 8.4 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 4.69 (s, 2H), 2.54 (s, 3H)
8-8		8A	8-1	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)-4-methoxybenzonitrile; LCMS [M+1] ⁺ = 384.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.01 (s, 1H), 9.29 (d, J = 2.0 Hz, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.63 (t, J = 2.0 Hz, 1H), 8.59 (br s, 3H), 8.45 - 8.36 (m, 3H), 7.98 (d, J = 8.8 Hz, 1H), 7.41 (d,

			J = 2.4 Hz, 1H), 7.24 (dd, J = 2.4, 8.8 Hz, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.94 (s, 3H)
8-9		8B 8-2	2-(5-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)pyridin-3-yl)terephthalonitrile LCMS [M+1]⁺ = 379.1; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 13.02 (s, 1H), 9.32 (d, J = 2.0 Hz, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.45 (m, 2H), 8.44 - 8.40 (m, 4H), 8.38 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.20 (dd, J = 1.6, 8.0 Hz, 1H), 4.60 (br d, J = 5.2 Hz, 2H)

PREPARATION of EXAMPLES 9-1 to 9-3

EXAMPLE 9-1



[0507] **Step 1:** A stirred solution of sodium borohydride (382 mg, 10.1 mmol, 2.60 *eq.*) in ethyl alcohol (150 mL) was treated portion-wise with methyl 7-bromo-4-oxo-3*H*-phthalazine-1-carboxylate **11c** (1.10 g, 3.89 mmol, 1.00 *eq.*) at 0 °C followed by a dropwise addition of a solution of calcium chloride (518 mg, 4.66 mmol, 1.20 *eq.*) in ethyl alcohol (150 mL). Stirring was continued for additional 3 hours at the 0 °C, and then 1 hour at 20 °C. After such time the reaction mixture was concentrated under reduced pressure and the residue was diluted with water (30 mL) and adjusted to pH 5 with 1N hydrochloric acid (5 mL). The resulting solid

was filtered and washed with water (5 mL $\times$ 3) and then triturated with ethyl alcohol (20 mL) to afford 6-bromo-4-(hydroxymethyl)-2*H*-phthalazin-1-one **12c** (990 mg, 3.88 mmol, 100% yield) as a white solid.

[0508] **Step 2:** To a solution of 6-bromo-4-(hydroxymethyl)-2*H*-phthalazin-1-one **12c** (300 mg, 1.18 mmol, 1.00 *eq.*) in DCE (10 mL) was added manganese dioxide (1.02 g, 11.8 mmol, 10.0 *eq.*) and the mixture was stirred at 80 °C for 12 hours. After such time the reaction mixture was filtered, and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 10:1 to 1:1) to give 7-bromo-4-oxo-3*H*-phthalazine-1-carbaldehyde **101** (73 mg, 288 μ mol, 25% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.66 (br s, 1H), 9.82 (s, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 8.22 - 8.18 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 2.0, 8.4 Hz, 1H).

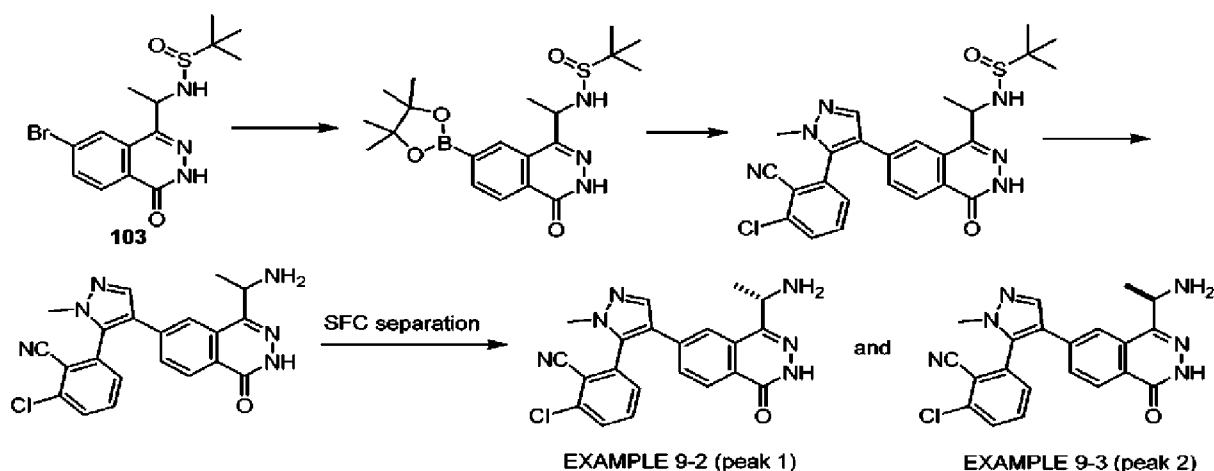
[0509] **Step 3:** To a solution of 7-bromo-4-oxo-3*H*-phthalazine-1-carbaldehyde **101** (300 mg, 1.19 mmol, 1.00 *eq.*) in THF (50 mL) was added titanium iso-propoxide (674 mg, 2.37 mmol, 700 μ L, 2.00 *eq.*) and 2-methylpropane-2-sulfinamide (216 mg, 1.78 mmol, 1.50 *eq.*) and the mixture was stirred at 60 °C for 12 hours. After such time the reaction mixture was quenched with water (1 mL) and the resulting solid was filtered. The filtrate was dried over sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate= 5/ 1 to 1/ 1) to give *N*-[(7-bromo-4-oxo-3*H*-phthalazin-1-yl)methylene]-2-methyl-propane-2-sulfinamide **102** (100 mg, 171 μ mol, 14% yield) as a white solid. LCMS [*M*+1]⁺ = 358.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.58 (br s, 1H), 9.32 (d, *J* = 2.0 Hz, 1H), 8.37 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.12 - 8.10 (dd, *J* = 2.0, 8.4 Hz, 1H), 1.26 (s, 9H).

[0510] **Step 4:** To a solution of *N*-[(7-bromo-4-oxo-3*H*-phthalazin-1-yl)methylene]-2-methyl-propane-2-sulfinamide **102** (100 mg, 281 μ mol, 1.00 *eq.*) in THF (5 mL) was added methylmagnesium bromide (3*M*, 281 μ L, 3.00 *eq.*) dropwise at -78 °C. The reaction mixture was then stirred at -78 °C for 2 hours. After such time the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 mL $\times$ 3). The combined organic portions were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-TLC (petroleum ether/ ethyl acetate= 10/ 1) to give *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)ethyl]-2-methyl-propane-2-sulfinamide **103** (40 mg, 98.2 μ mol, 35% yield) as a yellow solid. LCMS [*M*+1]⁺ = 374.2.

[0511] **Step 5:** A mixture of *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)ethyl]propane-2-sulfonamide **103** (35 mg, 94 μ mol, 1.00 *eq.*), 1-methyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **104** (35 mg, 122 μ mol, 1.30 *eq.*), Pd(dppf)Cl₂ (7 mg, 9 μ mol, 0.10 *eq.*), sodium carbonate (20 mg, 188 μ mol, 2.00 *eq.*) in water (0.2 mL) and dioxane (1 mL) was degassed and purged with nitrogen 3 times, and then stirred at 80 °C for 2 hours. After such time the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 mL $\times$ 3) and the combined organic phases were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-TLC (petroleum ether:ethyl acetate 1:1) to give 2-methyl-*N*-[1-[7-(1-methyl-5-phenyl-pyrazol-4-yl)-4-oxo-3*H*-phthalazin-1-yl]ethyl]propane-2-sulfonamide **105** (40 mg, 60 μ mol, 63% yield) as a brown oil. LCMS [M+1]⁺ = 450.4.

[0512] **Step 6:** A mixture of 2-methyl-*N*-[1-[7-(1-methyl-5-phenyl-pyrazol-4-yl)-4-oxo-3*H*-phthalazin-1-yl]ethyl]propane-2-sulfonamide **105** (36 mg, 80 μ mol, 1.00 *eq.*) and hydrochloric acid/ dioxane (4M, 9 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.05% hydrochloric acid)-ACN]; B%: 12%-32%, 6.5 min) to give 4-(1-aminoethyl)-6-(1-methyl-5-phenyl-pyrazol-4-yl)-2*H*-phthalazin-1-one, Example 9-1 (7 mg, 19 μ mol, 23% yield, HCl) as a white solid. LCMS [M+1]⁺ = 346.1. ¹H NMR (400 MHz, MeOD) δ = 8.30 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 7.91 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.66 - 7.60 (m, 3H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.50 - 7.45 (m, 2H), 4.66 - 4.53 (m, 1H), 3.81 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H).

EXAMPLES 9-2 & 9-3



[0513] **Step 1:** A mixture of (*R*)-*N*-(1-(7-bromo-4-oxo-3,4-dihydrophthalazin-1-yl)ethyl)-2-methylpropane-2-sulfonamide **103** (410 mg, 1.10 mmol, 1.00 *eq.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (839 mg, 3.30 mmol, 3.00 *eq.*), Pd(dppf)Cl₂ (81 mg, 0.11 mmol, 0.10 *eq.*) and potassium acetate (324 mg, 3.30 mmol, 3.00 *eq.*) in dioxane (10 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 0.5 hour under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether (40 mL) to give (*R*)-2-methyl-*N*-(1-(4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)ethyl)propane-2-sulfonamide (724 mg, crude) as a gray solid which used into the next step without further purification. LCMS [M-81]⁻ = 338.2.

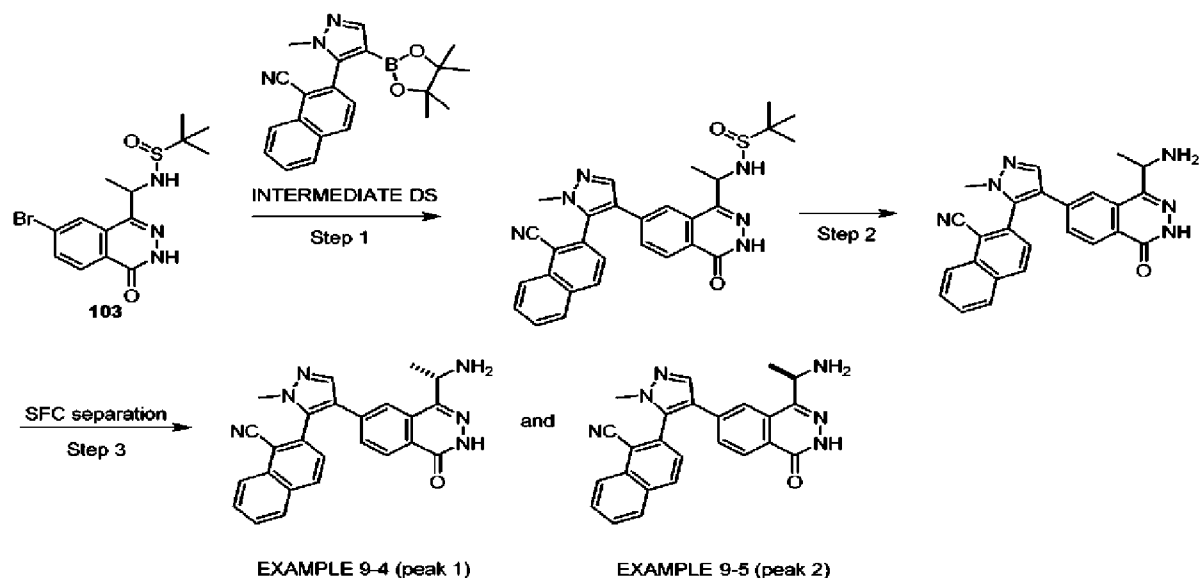
[0514] **Step 2:** A mixture of (*R*)-2-methyl-*N*-(1-(4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)ethyl)propane-2-sulfonamide (670 mg, 1.60 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-chloro-benzonitrile (308. mg, 1.04 mmol, 0.65 *eq.*), *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (104 mg, 0.160 mmol, 0.10 *eq.*), sodium carbonate (339 mg, 3.20 mmol, 2.00 *eq.*) in dioxane (10 mL) and water (2 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 0.5 hour under nitrogen atmosphere. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate = 1: 1 to 0: 1, dichloromethane: methyl alcohol = 10: 1) to give (*R*)-*N*-(1-(7-(5-(3-chloro-2-cyanophenyl)-1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydrophthalazin-1-yl)ethyl)-2-methylpropane-2-sulfonamide (281 mg, 0.552 mmol, 34% yield) as a brown solid. LCMS [M+1]⁺ = 509.2.

[0515] **Step 3:** To a solution of (*R*)-*N*-(1-(7-(5-(3-chloro-2-cyanophenyl)-1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydrophthalazin-1-yl)ethyl)-2-methylpropane-2-sulfonamide (140 mg, 0.275 mmol, 1.00 *eq.*) in hydrochloride/ dioxane (4.00 M, 5.4 mL) and the mixture was stirred at 15 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: [water (0.05% HCl)-ACN], B%: 12%-32%, 7 min) to give 2-[4-[4-(1-aminoethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-6-chloro-benzonitrile (40 mg, 0.097 mmol, 36% yield) as a yellow solid. LCMS [M+1]⁺ = 405.1; ¹H NMR (400 MHz,

CD₃OD) δ = 8.33 - 8.23 (m, 1H), 8.13 (d, J = 4.4 Hz, 1H), 8.02 - 7.84 (m, 2H), 7.82 - 7.66 (m, 2H), 7.64 - 7.57 (m, 1H), 4.87 (br s, 1H), 3.83 (d, J = 2.8 Hz, 3H), 1.54 - 1.41 (m, 3H).

[0516] **Step 4:** Enantiomers were separated by chiral SFC (DAICEL CHIRALPAK IC (250 mm $\times$ 30 mm, 10 μ m); mobile phase: [0.1% NH₄OH/EtOH]; B%: 50%-50%, 4.2 min; 46 min) followed by chiral SFC Chiralpak IC-3 (50 $\times$ 4.6 mm I.D., 3 μ m); Mobile phase: Phase A for CO₂, and Phase B for EtOH (0.05% DEA); Gradient elution: 50% EtOH (0.05% DEA) in CO₂ Flow rate: 3mL/min; Detector: PDA; Column Temp: 35 °C; Back Pressure: 100 Bar to give peak 1, Example 9-2, (11 mg, 0.025 mmol, 30% yield) as a yellow solid and peak 2, Example 9-3 (18 mg, 0.444 mmol, 50% yield) as an off-white solid. Each example was converted to the HCl salt. Example 9-2, Peak 1, single enantiomer, stereochemistry unassigned: LCMS [M+1] = 405.1; ¹H NMR (400 MHz, CD₃OD) δ = 8.31 (t, J = 8.4 Hz, 1H), 8.12 (d, J = 6.4 Hz, 1H), 7.92 - 7.87 (m, 2H), 7.80 - 7.67 (m, 3H), 4.88 - 4.84 (m, 1H), 3.83 (d, J = 1.2 Hz, 3H), 1.51 - 1.43 (m, 3H). Example 9-3, Peak 2, single enantiomer, stereochemistry unassigned: LCMS [M+1] = 405.1; ¹H NMR (400 MHz, CD₃OD) δ = 8.29 (dd, J = 8.2, 10.4 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.79 - 7.60 (m, 3H), 4.91 - 4.85 (m, 1H), 3.82 (d, J = 2.8 Hz, 3H), 1.52 - 1.41 (m, 3H).

EXAMPLES 9-4 & 9-5



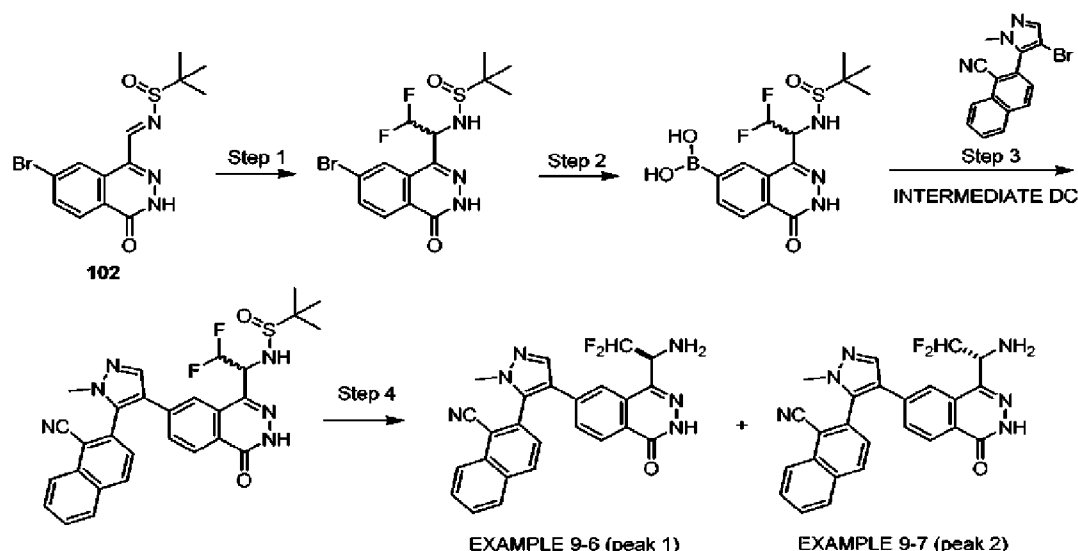
[0517] **Step 1:** A mixture of 2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]naphthalene-1-carbonitrile (80 mg, 0.222 mmol, 1.00 eq.), *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)ethyl]-2-methyl-propane-2-sulfonamide (100 mg, 0.267 mmol, 1.20

eq.), *ditert*-butyl(cyclopentyl)phosphane-dichloropalladium-iron (29 mg, 0.044 mmol, 0.20 *eq.*), potassium phosphate (142 mg, 0.668 mmol, 3.00*eq.*) in dioxane (4 mL) and water (0.8 mL) and was degassed and purged with nitrogen and then stirred at 100 °C for 1 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (Phenomenex Synergi C18 150 × 30 mm × 4 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 35%-64%, 11 min) to give *N*-[1-[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]ethyl]-2-methyl-propane-2-sulfinamide (48 mg, 0.091 mmol, 41% yield) was obtained as a white solid. LCMS [M+1]⁺ = 525.2.

[0518] **Step 2:** A mixture of *N*-[1-[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]ethyl]-2-methyl-propane-2-sulfinamide (40 mg, 0.076 mmol, 1.00 *eq.*) in HCl/dioxane (1 mL, 4 M) and methanol (1 mL) was stirred at 20 °C for 1 hour. The reaction mixture was the concentrated to give 2-[4-[4-(1-aminoethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (30 mg, crude) as a white solid which used into the next step without further purification. LCMS [M+1]⁺ = 421.2.

[0519] **Step 3:** SFC purification, Chiralpak IG-3 50 Å 4.6 mm, 3 μm Mobile phase: A: CO₂ B: ethanol (0.05% DEA) Isocratic: 40% B. Flow rate: 4 mL/min. Column temp. 35 °C. ABPR 1500 psi gave peak 1, Example 9-4 2-[4-[4-(1-aminoethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (12 mg, 29 μmol, 33% yield) as a white solid ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.42 (br s, 1H), 8.59 - 8.50 (m, 1H), 8.30 - 8.22 (m, 2H), 8.20 - 8.09 (m, 2H), 7.78 - 7.54 (m, 5H), 3.95 - 3.70 (m, 4H), 0.50 - 0.80 (m, 3H). And peak 2, Example 9-5 and 2-[4-[4-(1-aminoethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (12 mg, 29 μmol, 33% yield) as a white solid ¹H NMR (400MHz, DMSO-*d*₆) δ = 12.41 (br s, 1H), 8.60 - 8.50 (m, 1H), 8.30 - 8.23 (m, 2H), 8.19 - 8.09 (m, 2H), 7.92 - 7.54 (m, 6H), 3.90 - 3.70 (m, 4H), 0.83 - 0.55 (m, 3H).

EXAMPLES 9-6 & 9-7



[0520] **Step 1:** To a solution of *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)methylene]-2-methyl-propane-2-sulfinamide (276 mg, 0.775 mmol, 1.00 *eq.*) and difluoromethyl(trimethyl)silane (289 mg, 2.32 mmol, 3.00 *eq.*) in THF (2.0 mL) was added potassium *tert*-butoxide (1 M, 2.3 mL, 3.00 *eq.*) and the mixture was stirred at -78°C for 12 hours. The reaction mixture was then quenched with water (2 mL) and extracted with ethyl acetate (2 mL $\times$ 3). The combined organic phase were then washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 10: 1) to give *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)-2,2-difluoro-ethyl]-2-methyl-propane-2-sulfinamide (107 mg, 0.182 mmol, 24% yield) as a black solid. LCMS $[M+1]^+ = 410.1$; ¹H NMR (400 MHz, CDCl₃-*d*) δ = 10.58 - 10.26 (m, 1H), 8.29 - 8.22 (m, 1H), 8.06 (s, 1H), 7.93 - 7.86 (m, 1H), 6.22 - 5.86 (m, 1H), 4.72 (d, *J* = 7.2 Hz, 1H), 1.30 (s, 9H).

[0521] **Step 2:** A mixture of *N*-[1-(7-bromo-4-oxo-3*H*-phthalazin-1-yl)-2,2-difluoro-ethyl]-2-methyl-propane-2-sulfinamide (97 mg, 0.238 mmol, 1.00 *eq.*), bis(pinacolato)diboron (78 mg, 0.309 mmol, 1.30 *eq.*), Pd(dppf)Cl₂ (17 mg, 0.024 mmol, 0.10 *eq.*), potassium acetate (67 mg, 0.713 mmol, 3.00 *eq.*) in dioxane (1.0 mL) was degassed and purged with nitrogen 3 times, and then stirred at 100 °C for 1 hour. The mixture was then concentrated under reduced pressure to give 4-[1-(*tert*-butylsulfinylamino)-2,2-difluoro-ethyl]-1-oxo-2*H*-phthalazin-6-yl]boronic acid (100 mg, crude) as a black solid. LCMS $[M+1]^+ = 374.1$.

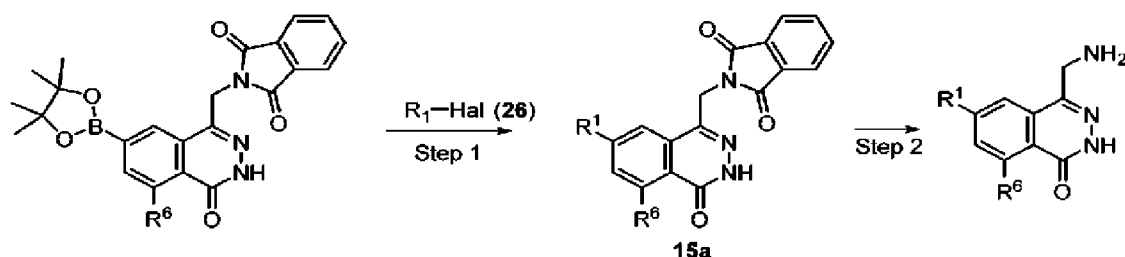
[0522] **Step 3:** A mixture of [4-[1-(tert-butylsulfinylamino)-2,2-difluoro-ethyl]-1-oxo-2*H*-phthalazin-6-yl]boronic acid (100 mg, crude), 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (77 mg, 0.247 mmol), sodium bicarbonate (62 mg, 0.740 mmol), *ditert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (16 mg, 0.024 mmol, 0.10 *eq.*) in dioxane (3.0 mL) and water (0.6 mL) was degassed and purged with nitrogen 3 times, and then stirred at 100 °C for 2 hours under nitrogen atmosphere. The mixture was then concentrated under reduced pressure and the residue was purified by prep-TLC (dichloromethane: methyl alcohol 10: 1) to give *N*-[1-[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]-2,2-difluoro-ethyl]-2-methyl-propane-2-sulfinamide (36 mg, 0.037 mmol, 15% yield) as a yellow solid. LCMS $[M+1]^+ = 561.2$.

[0523] **Step 4:** A mixture of *N*-[1-[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]-2,2-difluoro-ethyl]-2-methyl-propane-2-sulfinamide (30 mg, 0.053 mmol, 1.00 *eq.*) in hydrochloric acid/ dioxane (1.0 mL) was degassed and purged with nitrogen 3 times, and the mixture stirred at 0 °C for 2 hours. The mixture was then concentrated and the residue purified by prep-HPLC (Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: [water (0.05% hydrochloric acid)-ACN]; B%: 18%-38%, 7 min) then further separated by SFC (Daicel ChiralPak IG (250 × 30 mm, 10 μm); mobile phase: [Mobile phase: A: CO₂ B: ACN/ EtOH (0.1% NH₃•water)] isocratic 60%, 50 min) to give Example 9-6, 2-[4-[4-[(1*S*)-1-amino-2,2-difluoro-ethyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (5.2 mg, 0.011 mmol, 21% yield) as a brown solid and Example 9-7, 2-[4-[4-[(1*R*)-1-amino-2,2-difluoro-ethyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (4.3 mg, 0.009 mmol, 17% yield) as a brown solid. Example 9-6: LCMS $[M+1]^+ = 457.1$; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.61 (br d, *J* = 3.6 Hz, 1H), 8.53 (dd, *J* = 8.8, 10.4 Hz, 1H), 8.29 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.14 (dd, *J* = 8.2, 14.4 Hz, 1H), 8.07 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.92 - 7.74 (m, 4H), 7.63 (ddd, *J* = 1.6, 8.4, 17.2 Hz, 1H), 6.14 - 5.59 (m, 1H), 4.17 - 3.95 (m, 1H), 3.78 (d, *J* = 1.6 Hz, 3H), 3.31 (br s, 2H). ¹H NMR (400 MHz, MeOD) δ = 8.43 (dd, *J* = 8.4, 18.0 Hz, 1H), 8.30 - 8.11 (m, 4H), 7.89 - 7.61 (m, 5H), 5.95 - 5.29 (m, 1H), 4.13 - 3.98 (m, 1H), 3.84 (d, *J* = 2.4 Hz, 3H). Example 9-7: LCMS $[M+1]^+ = 457.0$; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.71 - 12.36 (m, 1H), 8.58 - 8.48 (m, 1H), 8.29 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.14 (dd, *J* = 8.0, 14.4 Hz, 1H), 8.07 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.93 - 7.74 (m, 4H), 7.63 (ddd, *J* = 1.6, 8.4, 17.2 Hz, 1H), 6.10 - 5.59 (m, 1H), 4.10 (q, *J* = 5.6 Hz, 1H), 3.78 (d, *J* = 1.6 Hz, 3H), 3.31 (br s, 2H). ¹H NMR (400 MHz,

MeOD) δ = 8.44 (dd, J = 8.4, 17.6 Hz, 1H), 8.29 - 8.12 (m, 4H), 7.90 - 7.62 (m, 5H), 5.94 - 5.36 (m, 1H), 4.12 - 4.06 (m, 1H), 3.85 (d, J = 2.4 Hz, 3H).

COUPLING METHOD (CM) AND PURIFICATION METHODS (PM) FOR THE PREPARATION OF EXAMPLES IN TABLE 10

GENERAL COUPLING METHOD 10A



R^6 = Cl INTERMEDIATE DK

R^6 = F INTERMEDIATE DL

R^6 = CH₃ INTERMEDIATE DM

R^6 = CF₃ INTERMEDIATE EG

R^6 = OCH₃ INTERMEDIATE EX

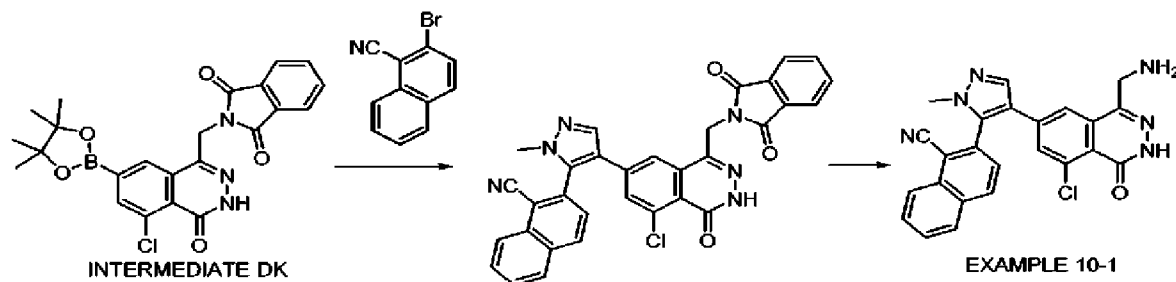
wherein R^1 = aryl or heteroaryl and Hal = Cl, Br, I

[0524] **Step 1:** A mixture of the appropriate aryl/heteroaryl-halide **26** (390 μ mol, 1.5 *eq.*), intermediate AN (260 μ mol, 1.00 *eq.*), palladium catalyst such as Pd(dppf)Cl₂, Pd(dtbpf)Cl₂ or Ad₂n-BuP)-Pd (26.0 μ mol, 0.10 *eq.*), sodium bicarbonate (0.521 μ mol, 2.0-3.0 *eq.*) in dioxane (1.0 mL) and water (0.2 mL) was purged with nitrogen 3 times. The mixture was then stirred at 80 °C for 2 hours. After such time the mixture was purified using the methods described for CM 10A-1 or CM 10A-2 to give coupling product **15a**.

[0525] **Step 2:** To a solution of corresponding coupling product **15a** in ethyl alcohol (1.0 mL) was added hydrazine hydrate (20 *eq.*). The mixture was stirred at 80 °C for 1 hour. After such time the mixture was concentrated in vacuo and the residue purified by prep-HPLC according to one of the purification methods (PM) 4-1 through 4-13.

CM 10A-1

EXAMPLE 10-1

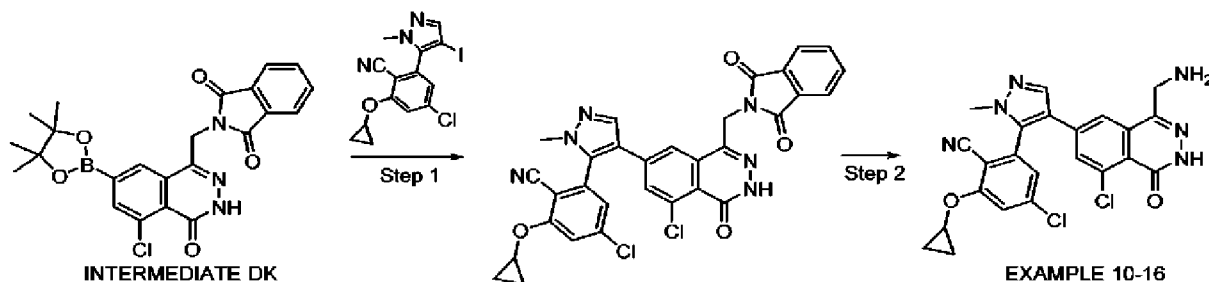


[0526] **Step 1:** A mixture of 2-((5-chloro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl)isoindoline-1,3-dione, Intermediate DK (35 mg, 0.75 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (24 mg, 0.75 mmol, 1.00 *eq.*), Pd(dtbpf)Cl₂ (4.9 mg, 0.08 mmol, 0.10 *eq.*), sodium bicarbonate (19 mg, 0.23 mmol, 3.00 *eq.*) in dioxane (2.0 mL) and water (0.4 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 2 hours. The mixture was then concentrated under reduced pressure and the residue purified by prep-TLC (SiO₂, dichloromethane/methyl alcohol 10:1) to give 2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (20 mg, 0.035 mmol, 47% yield) as a yellow solid. LCMS [M+1]⁺ = 571.2.

[0527] **Step 2:** A mixture of 2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (15 mg, 0.026 mmol, 1.00 *eq.*) and hydrazine hydrate (0.525 mmol, 25 μL, 20.0 *eq.*) in ethyl alcohol (0.8 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 1 hour. The mixture was then concentrated and the residue purified by prep-HPLC methods PM 4-6 to give 2-[4-[4-(aminomethyl)-8-chloro-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile, Example 10-1 (10 mg, 0.018 mmol, 69% yield) as an off-white solid.

CM 10A-2

EXAMPLE 10-16



[0528] **Step 1:** A mixture of 4-chloro-2-(cyclopropoxy)-6-(4-iodo-2-methyl-pyrazol-3-yl)benzonitrile, Intermediate DK (18 mg, 0.45 mmol, 1.00 *eq.*), 2-[[5-chloro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-phthalazin-1-yl]methyl]isoindoline-1,3-dione (25 mg, 0.54 mmol, 1.20 *eq.*), sodium bicarbonate (11 mg, 0.13 mmol, 3.00 *eq.*), [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate ($\text{Ad}_2\text{n-BuP}$)-Pd (3.3 mg, 0.005 mmol, 0.10 *eq.*) in water (0.2 mL) and dioxane (1.0 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 80 °C for 2 hours. After such time the reaction mixture was concentrated and the residue was diluted with ethyl acetate (30 mL) and washed with brine (40 mL $\times$ 3), dried over sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate = 3: 1) to give 4-chloro-2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-6-(cyclopropoxy)benzonitrile (20 mg, 0.032 mmol, 73% yield) as a yellow solid. LCMS $[\text{M}+\text{H}]^+ = 611.1$.

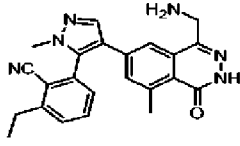
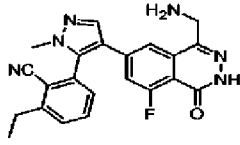
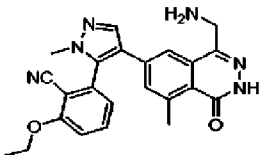
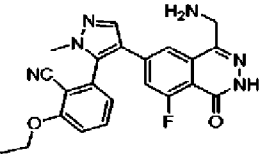
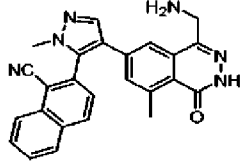
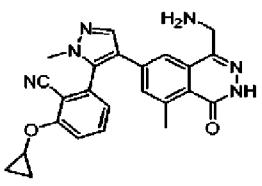
[0529] **Step 2:** To a solution of 4-chloro-2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-6-(cyclopropoxy)benzonitrile (15 mg, 0.025 mmol, 1.00 *eq.*) in ethyl alcohol (2 mL) was added hydrazine hydrate (2.5 mg, 0.049 mmol, 2.00 *eq.*). The mixture was stirred at 25 °C for 2 hours. The pH of the reaction mixture was then adjusted to pH 7 with hydrochloric acid (6.0 M, 0.5 mL), then concentrated and the residue was purified by prep-HPLC methods PM 4-6 to give 2-[4-[4-(aminomethyl)-8-chloro-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-4-chloro-6-(cyclopropoxy)benzonitrile (3 mg, 0.005 mmol, 21% yield, HCl) as a yellow gum.

[0530] Following the teachings of the General Reaction Schemes, the general coupling method CM 10A-1 and CM 10A-2 and using purification methods 4-4 to 4-6, the synthesis of

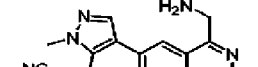
Example 10-1, Example 10-16 and the Intermediates disclosed herein, the Examples 10-1 to 10-20 are prepared as shown in Table 10.

Table 10

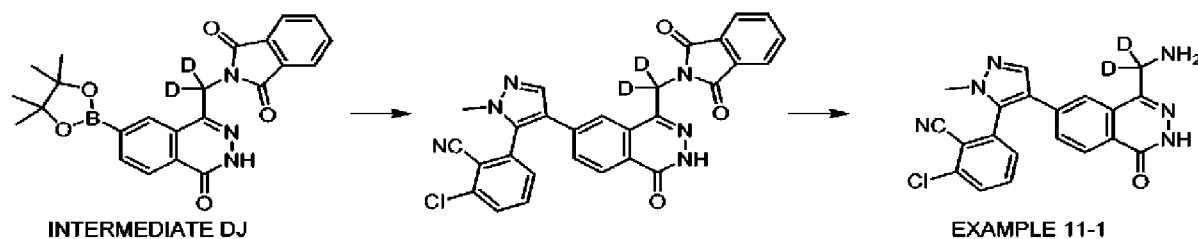
Example	Structure	CM	PM	Compound Name and Characterization
10-1		10A-1	4-4	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS [M+1] ⁺ = 441.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.81 (s, 1H), 8.57 (br d, <i>J</i> = 8.4 Hz, 1H), 8.42 (s, 1H), 8.40 - 8.24 (m, 4H), 8.16 (br d, <i>J</i> = 8.0 Hz, 1H), 7.95 - 7.81 (m, 3H), 7.72 (s, 1H), 7.30 (s, 1H), 4.33 - 4.02 (m, 2H), 3.78 (s, 3H)
10-2		10A-1	4-4	2-(4-(4-(aminomethyl)-8-fluoro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS [M+1] ⁺ = 425.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.81 (s, 1H), 8.57 (d, 1H), 8.39 (s, 1H), 8.30 - 8.25 (m, 4H), 8.15 (d, <i>J</i> = 8.0 Hz, 1H), 7.93 - 7.80 (m, 3H), 7.60 (s, 1H), 7.05 (d, 1H), 4.27 - 4.08 (m, 2H), 3.78 (s, 3H)
10-3		10A-1	4-5	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chlorobenzonitrile LCMS [M+1] ⁺ = 425.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.39 - 8.31 (m, 4H), 8.04 - 7.96 (m, 2H), 7.84 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 7.59 (d, <i>J</i> = 1.6 Hz, 1H), 7.42 (d, <i>J</i> = 1.6 Hz, 1H), 4.27 - 4.12 (m, 2H), 3.77 (s, 3H)
10-4		10A-1	4-5	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethylbenzonitrile LCMS [M+1] ⁺ = 419.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.82 (s, 1H), 8.48 (br s, 3H), 8.42 (s, 1H), 7.91 (t, <i>J</i> = 8.0 Hz, 1H), 7.77 (d, <i>J</i> = 7.6 Hz, 1H), 7.65 (d, <i>J</i> = 7.6 Hz, 1H), 7.58 (d, <i>J</i> = 1.6 Hz, 1H), 7.34 (s, 1H), 4.23 - 4.06 (m, 2H), 3.73 (s, 3H), 2.87 (q, <i>J</i> = 7.6 Hz, 2H), 1.24 (t, <i>J</i> = 7.6 Hz, 3H)
10-5		10A-1	4-5	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethoxybenzonitrile LCMS [M+1] ⁺ = 435.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.84 (s, 1H), 8.44 - 8.26 (m, 4H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H), 7.61 (br d, <i>J</i> = 4.8 Hz, 1H), 7.50 (d, <i>J</i> = 8.8 Hz, 1H), 7.40 (br d, <i>J</i> = 2.8 Hz, 1H), 7.32 (d, <i>J</i> = 7.6 Hz, 1H), 4.37 - 4.27 (m, 2H), 4.25 - 4.06 (m, 2H), 3.72 (s, 3H), 1.38 (t, <i>J</i> = 7.2 Hz, 3H)
10-6		10A-1	4-5	2-(4-(4-(aminomethyl)-8-fluoro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chlorobenzonitrile LCMS [M+1] ⁺ = 409.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.39 - 8.28 (m, 4H), 8.04 - 7.93 (m, 2H), 7.81 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 7.44

				(s, 1H), 7.24 (d, $J = 12.4$ Hz, 1H), 4.25 - 4.12 (m, 2H), 3.76 (s, 3H)
10-7		10A-1	4-4	2-(4-(4-(aminomethyl)-8-methyl-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethylbenzonitrile LCMS $[M+1]^+ = 399.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.64$ (s, 1H), 8.31 (s, 4H), 7.92 - 7.85 (m, 1H), 7.75 (d, $J = 7.2$ Hz, 1H), 7.62 (dd, $J = 0.8$, 7.6 Hz, 1H), 7.39 (s, 1H), 7.23 (s, 1H), 4.18 - 4.01 (m, 2H), 3.74 (s, 3H), 2.87 (q, $J = 7.6$ Hz, 2H), 2.64 (s, 3H), 1.24 (t, $J = 7.6$ Hz, 3H)
10-8		10A-1	4-4	2-(4-(4-(aminomethyl)-8-fluoro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethylbenzonitrile LCMS $[M+1]^+ = 403.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.82$ (s, 1H), 8.48 (br s, 3H), 8.39 (s, 1H), 7.90 (t, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 0.8$ Hz, 1H), 7.18 (d, $J = 12.4$ Hz, 1H), 4.20 - 3.99 (m, 2H), 3.73 (s, 3H), 2.88 (q, $J = 7.6$ Hz, 2H), 1.24 (t, $J = 7.6$ Hz, 3H)
10-9		10A-1	4-4	2-(4-(4-(aminomethyl)-8-methyl-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethoxybenzonitrile LCMS $[M+1]^+ = 415.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.64$ (s, 1H), 8.37 - 8.26 (m, 3H), 7.87 (dd, $J = 7.6$, 8.8 Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.41 (s, 1H), 7.35 - 7.26 (m, 2H), 4.30 (dq, $J = 2.8$, 6.8 Hz, 2H), 4.21 - 4.01 (m, 2H), 3.72 (s, 3H), 2.67 (s, 3H), 1.39 (t, $J = 7.2$ Hz, 3H)
10-10		10A-1	4-4	2-(4-(4-(aminomethyl)-8-fluoro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-ethoxybenzonitrile LCMS $[M+1]^+ = 419.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.84$ (s, 1H), 8.45 - 8.25 (m, 4H), 7.89 (dd, $J = 7.6$, 8.4 Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 12.4$ Hz, 1H), 4.35 - 4.26 (m, 2H), 4.25 - 4.07 (m, 2H), 3.72 (s, 3H), 1.39 (t, $J = 6.8$ Hz, 3H)
10-11		10A-1	4-6	2-(4-(4-(aminomethyl)-8-methyl-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS $[M+1]^+ = 421.1$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.60$ (s, 1H), 8.56 (d, $J = 8.4$ Hz, 1H), 8.42 (br s, 3H), 8.34 (s, 1H), 8.29 (d, $J = 7.6$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.93 - 7.82 (m, 3H), 7.54 (s, 1H), 7.19 (s, 1H), 4.25 - 4.12 (m, 1H), 4.07 - 3.94 (m, 1H), 3.77 (s, 3H), 2.52 (s, 3H)
10-12		10A-1	4-6	2-(4-(4-(aminomethyl)-8-methyl-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxybenzonitrile LCMS $[M+1]^+ = 427.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.63$ (s, 1H), 8.44 (br s, 3H), 8.28 (s, 1H), 7.93 (dd, $J = 7.6$, 8.8 Hz, 1H), 7.75 (dd, $J = 0.8$, 8.8 Hz, 1H), 7.37 (d, $J = 1.2$ Hz, 1H), 7.35 (dd, $J = 0.8$, 7.6 Hz, 1H), 7.31 (s, 1H), 4.22 - 4.09 (m, 2H), 4.08 - 3.95 (m, 1H), 3.72 (s, 3H), 2.67 (s, 3H), 0.94 - 0.86 (m, 2H), 0.83 - 0.74 (m, 2H)

10-13		10A-1	4-6	2-(4-(4-(aminomethyl)-1-oxo-8-(trifluoromethyl)-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile LCMS [M+1] ⁺ = 475.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.98 (s, 1H), 8.58 (d, <i>J</i> = 8.4 Hz, 1H), 8.52 (s, 1H), 8.39 (br d, <i>J</i> = 1.2 Hz, 3H), 8.30 (d, <i>J</i> = 7.6 Hz, 1H), 8.19 (s, 1H), 8.14 (d, <i>J</i> = 8.0 Hz, 1H), 7.93 - 7.84 (m, 3H), 7.53 (s, 1H), 4.48 - 4.24 (m, 2H), 3.80 (s, 3H)
10-14		10A-1	4-6	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxybenzonitrile LCMS [M+1] ⁺ = 447.2; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.47 (br s, 3H), 8.38 (s, 1H), 7.96 (dd, <i>J</i> = 7.7, 8.6 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.57 (d, <i>J</i> = 1.6 Hz, 1H), 7.42 (d, <i>J</i> = 1.6 Hz, 1H), 7.39 (dd, <i>J</i> = 0.6, 7.6 Hz, 1H), 4.26 - 4.16 (m, 2H), 4.15 - 4.06 (m, 1H), 3.73 (s, 3H), 0.94 - 0.76 (m, 4H)
10-15		10A-1	4-6	2-(4-(4-(aminomethyl)-8-methyl-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 439.2; ¹ H NMR (400 MHz, DMSO - <i>d</i> ₆) δ = 12.15 (s, 1H), 8.53 (d, <i>J</i> = 10.0 Hz, 1H), 8.31 (s, 1H), 8.27 - 8.23 (m, 1H), 8.19 - 8.13 (m, 1H), 7.92 - 7.83 (m, 2H), 7.53 (d, <i>J</i> = 0.8 Hz, 1H), 7.38 (d, <i>J</i> = 1.6 Hz, 1H), 3.81 (s, 3H), 3.35 (br s, 2H), 2.69 (s, 3H)
10-16		10A-2	4-6	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxybenzonitrile LCMS [M+H] ⁺ = 481.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.86 (s, 1H), 8.45 (br s, 3H), 8.36 (s, 1H), 7.85 (d, <i>J</i> = 1.6 Hz, 1H), 7.61 (d, <i>J</i> = 1.2 Hz, 2H), 7.43 (d, <i>J</i> = 1.2 Hz, 1H), 4.30 - 4.23 (m, 2H), 4.19 (br d, <i>J</i> = 4.4 Hz, 1H), 3.76 (s, 3H), 0.96 - 0.88 (m, 2H), 0.75 - 0.85 (m, 2H)
10-17		10A-2	4-6	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 459.1; ¹ H NMR (400 MHz, DMSO - <i>d</i> ₆) δ = 12.82 (s, 1H), 8.58 (d, <i>J</i> = 10.0 Hz, 1H), 8.52 (s, 1H), 8.49 (br s, 3H), 8.31 - 8.26 (m, 1H), 8.20 - 8.14 (m, 1H), 7.92 - 7.85 (m, 2H), 7.76 (d, <i>J</i> = 1.6 Hz, 1H), 7.30 (d, <i>J</i> = 1.6 Hz, 1H), 4.35 - 4.06 (m, 2H), 3.82 (s, 3H)
10-18		10A-2	4-6	2-(4-(4-(aminomethyl)-8-fluoro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-3-fluoro-1-naphthonitrile LCMS [M+1] ⁺ = 443.1
10-19		10A-2	4-6	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-methylbenzonitrile LCMS [M+1] ⁺ = 461.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.83 (s, 1H), 8.50 (br s, 3H), 8.38 (s, 1H), 7.61 (s, 1H), 7.53 (d, <i>J</i> = 1.6 Hz, 1H), 7.49 (s, 1H), 7.23 (s, 1H), 4.23 - 4.12 (m, 2H),

				4.11 - 4.01 (m, 1H), 3.72 (s, 3H), 2.53 (s, 3H), 0.94 - 0.86 (m, 2H), 0.80 - 0.74 (m, 2H)
10-20		10A-1	4-6	2-(4-(4-(aminomethyl)-8-chloro-1-oxo-1,2-dihydropthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-3-fluoro-4-methylbenzonitrile LCMS [M+1] ⁺ = 479.1; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.85 (s, 1H), 8.52 (br s, 3H), 8.46 (s, 1H), 7.80 (d, <i>J</i> = 6.0 Hz, 1H), 7.54 (d, <i>J</i> = 1.6 Hz, 1H), 7.50 (d, <i>J</i> = 1.6 Hz, 1H), 4.27 - 4.05 (m, 3H), 3.76 (s, 3H), 2.48 (d, <i>J</i> = 1.6 Hz, 3H), 0.94 - 0.85 (m, 2H), 0.83 - 0.68 (m, 2H)

EXAMPLE 11-1

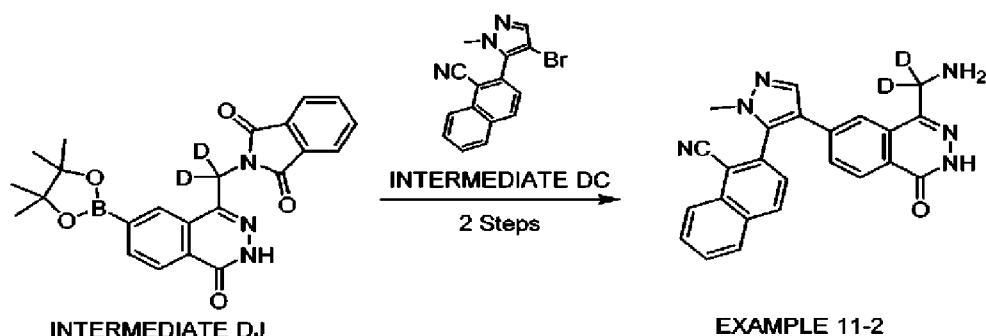


[0531] **Step 1:** A mixture of 2-((4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydrophthalazin-1-yl)methyl-d2)isoindoline-1,3-dione, Intermediate DJ (100 mg, 0.152 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)-6-chloro-benzonitrile (58 mg, 0.197 mmol, 1.30 *eq.*), Pd(dtbpf)Cl₂ (10 mg, 0.015 mmol, 0.10 *eq.*) and sodium bicarbonate (38 mg, 0.455 mmol, 3.00 *eq.*) in dioxane (3.0 mL) and water (0.6 mL) was degassed and purged with nitrogen 3 times and stirred at 80 °C for 2 hours. After such time the mixture was concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 10/1 to 0/1) to give 2-chloro-6-(4-(4-((1,3-dioxoisindolin-2-yl)methyl-d2)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzonitrile (50 mg, 0.089 mmol, 59% yield) as a yellow solid. LCMS [M+1]⁺ = 523.1.

[0532] **Step 2:** A mixture of 2-chloro-6-(4-(4-((1,3-dioxoisindolin-2-yl)methyl-d2)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)benzonitrile (50 mg, 0.089 mmol, 1.00 *eq.*) and hydrazine hydrate (0.044 mL, 0.89 mmol, 10.0 *eq.*) in ethyl alcohol (2 mL) was stirred at 80 °C for 1 hour under nitrogen atmosphere. After such time the mixture was concentrated under reduced pressure and the residue purified by prep-HPLC (Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% trifluoroacetic acid)-ACN]; B%: 7%-37%, 10 min). to give 2-(4-(4-(aminomethyl-d2)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-chlorobenzonitrile (31 mg, 0.059 mmol, 66% yield) as a white

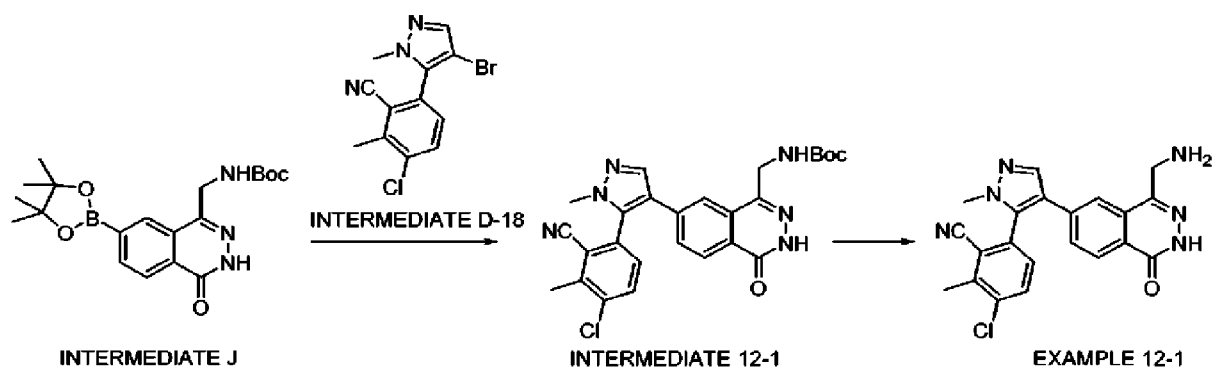
solid. LCMS $[M+1]^+ = 393.1$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.88$ (s, 1H), 8.34 (br s, 3H), 8.28 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 8.00 - 7.97 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.97 - 7.92 (t, $J = 7.2$ Hz, 1H), 7.79 - 7.76 (m, 2H), 7.43 (dd, $J = 1.6, 8.4$ Hz, 1H), 3.76 (s, 3H).

EXAMPLE 11-2



[0533] 2-(4-(4-(aminomethyl-d₂)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-1-naphthonitrile, Example 11-2 was prepared as a white solid (19 mg, 0.046 mmol, 35% yield) following the same procedure as example 11-1 using intermediate DJ (60 mg, 0.138 mol, 1.00 *eq.*) and Intermediate DC 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (56 mg, 0.18 mmol, 1.30 *eq.*). LCMS $[M+1]^+ = 409.3$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.85$ (s, 1H), 8.53 (d, $J = 8.4$ Hz, 1H), 8.33 - 8.27 (m, 4H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.92 - 7.82 (m, 4H), 7.32 (dd, $J = 1.6, 8.0$ Hz, 1H), 3.78 (s, 3H).

EXAMPLE 12-1

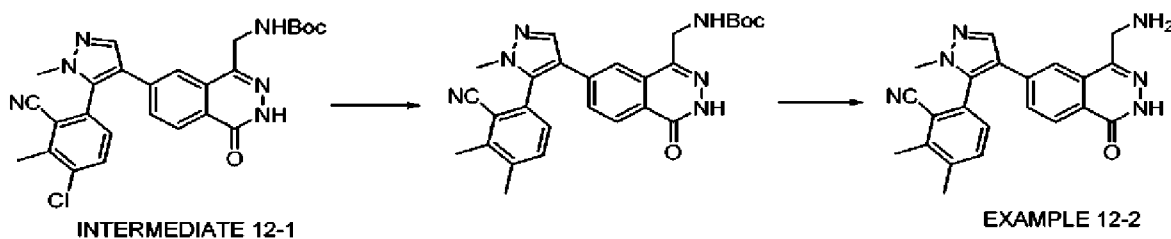


[0534] **Step 1:** A mixture of 6-(4-bromo-2-methyl-pyrazol-3-yl)-3-chloro-2-methyl-benzonitrile, Intermediate D-18 (200 mg, 0.64 mmol, 1.00 *eq.*), intermediate J, (310 mg, 0.77 mmol, 1.20 *eq.*), sodium bicarbonate (108 mg, 1.29 mmol, 2.00 *eq.*) and Pd(dtbpf)Cl₂ (42 mg,

0.064 mmol, 0.10 *eq.*) in dioxane (3 mL) and water (0.6 mL) was degassed with nitrogen and stirred at 80 °C for 1 hour. After such time the mixture was concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane/methyl alcohol 20/1) to give *tert*-butyl *N*-[[7-[5-(4-chloro-2-cyano-3-methyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate 12-1 (150 mg, 0.30 mmol, 46% yield) as a yellow solid. LCMS [M+1]⁺ = 505.2.

[0535] **Step 2:** To a solution of *tert*-butyl ((7-(5-(4-chloro-2-cyano-3-methylphenyl)-1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)carbamate (50 mg, 0.10 mmol, 1.00 *eq.*) in dichloromethane (1.5 mL) was added trifluoroacetic acid (0.4 mL). The mixture was stirred at 25 °C for 0.5 hour, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 22%-32%, 7 min) to give 6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-3-chloro-2-methylbenzonitrile, Example 12-1 (14 mg, 0.026 μmol, 27% yield) as a white solid. LCMS [M+1]⁺ = 405.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.87 (s, 1H), 8.55 - 8.34 (br s, 3H), 8.28 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 4.35 (br s, 2H), 3.73 (s, 3H), 2.58 (s, 3H).

EXAMPLE 12-2

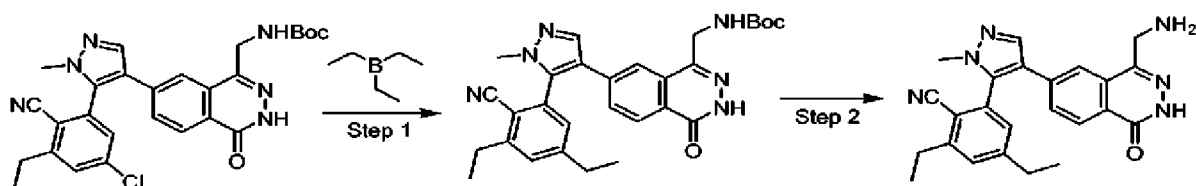


[0536] **Step 1:** A mixture of Intermediate 12-1 (50 mg, 0.10 mmol, 1.00 *eq.*), methylboronic acid (18 mg, 0.30 mmol, 3.00 *eq.*), Pd(dtbpf)Cl₂ (6.5 mg, 0.010 mmol, 0.10 *eq.*) and potassium carbonate (41 mg, 0.30 mmol, 3.00 *eq.*) in dioxane (2 mL) was degassed with nitrogen and stirred at 100 °C for 1 hour. After such time the mixture was concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane/methyl alcohol 20/1) to give *tert*-butyl *N*-[[7-[5-(2-cyano-3,4-dimethyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (30 mg, 0.062 mmol, 63% yield) as a yellow solid. LCMS [M+1]⁺ = 485.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.22 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H),

7.99 (s, 1H), 7.60 (s, 1H), 7.57 - 7.46 (m, 2H), 7.20 (d, $J = 7.6$ Hz, 1H), 5.42 - 5.33 (m, 1H), 3.81 (s, 3H), 3.50 (s, 2H), 2.59 (s, 3H), 2.46 (s, 3H), 1.49 (s, 9H).

[0537] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(2-cyano-3,4-dimethyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (30 mg, 0.062 mmol, 1.00 *eq.*) in dichloromethane (1.5 mL) was added trifluoroacetic acid (0.5 mL). The mixture was stirred at 25°C for 0.5 hour then concentrated in vacuum. The formed residue was purified by prep-HPLC (Column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 6%-36%, 10 min) to give 6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-2,3-dimethylbenzonitrile, Example 12-2 (7.8 mg, 0.016 mmol, 25% yield) as a white solid. LCMS $[M+1]^+ = 385.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.84$ (s, 1H), 8.32 (br s, 3H), 8.26 (s, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.74 - 7.65 (m, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 4.26 (br d, $J = 1.2$ Hz, 2H), 3.70 (s, 3H), 2.48 (br s, 3H), 2.42 (s, 3H).

EXAMPLE 12-3

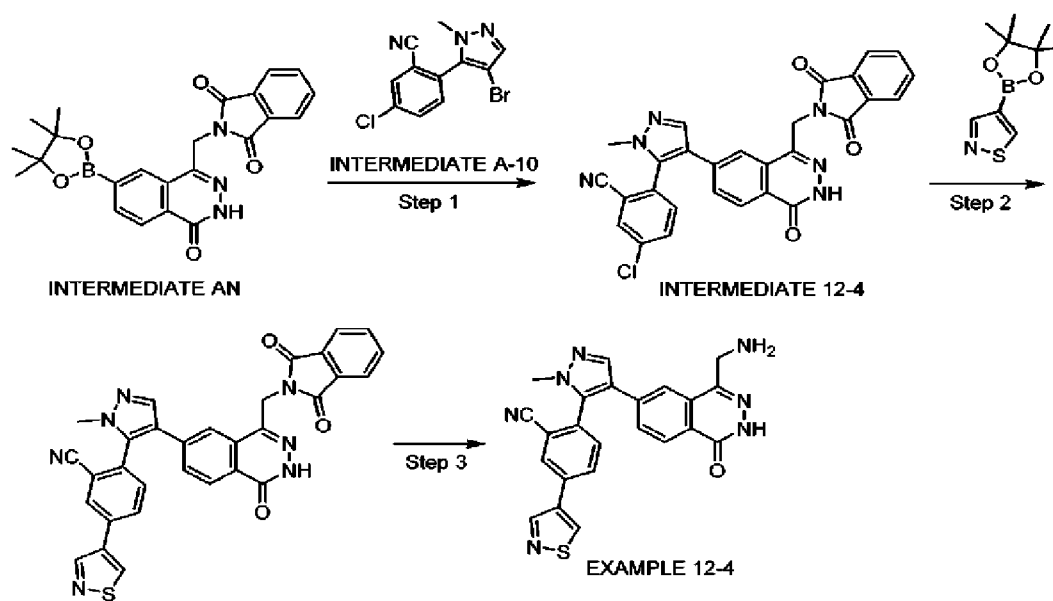


[0538] **Step 1:** To a solution of *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-3-ethyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (80 mg, 0.154 mmol, 1.00 *eq.*) and triethylborane (1.00 M, 0.450 mmol, 3.00 *eq.*) in THF (5 mL) and water (0.5 mL) was added potassium carbonate (64 mg, 0.462 mmol, 3.00 *eq.*) and XPhos Pd G3 (13 mg, 15 μmol, 0.10 *eq.*). The mixture was stirred at 85 °C for 8 hours then concentrated and the residue was diluted with water (10 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane: methanol 20: 1) to give *tert*-butyl *N*-[[7-[5-(2-cyano-3,5-diethyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (40 mg crude) as a white solid. LCMS $[M+1]^+ = 513.5$.

[0539] **Step 2:** To a mixture of *tert*-butyl *N*-[[7-[5-(2-cyano-3,5-diethyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (40 mg, 78 μmol, 1.00 *eq.*) in

dichloromethane (2 mL) was added trifluoroacetic acid (0.8 mL) in one portion at 0 °C under a nitrogen atmosphere. The mixture was stirred at 20 °C for 1 hour then concentrated under reduced pressure and the formed residue was purified by Prep-HPLC (Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% TFA)-ACN]; B%: 17%-47%, 10 min) and further purified by SFC (DAICEL CHIRALCEL OD-H (250 mm × 30 mm, 5 μm); mobile phase: [0.1% NH₃H₂O EtOH]; B%: 40%) to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-4,6-diethyl-benzonitrile, Example 12-3 (14 mg, 34 μmol, 70% yield) as a light yellow solid. LCMS [M+1]⁺ = 413.3; ¹H NMR (400 MHz, CDCl₃) δ = 8.27 (br d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.54 (br d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 7.13 (s, 1H), 3.88 (br s, 2H), 3.82 (s, 3H), 2.91 (q, *J* = 8.0 Hz, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 2.12 - 1.99 (m, 2H), 1.32 (br t, *J* = 7.6 Hz, 3H), 1.28 - 1.23 (m, 3H).

EXAMPLE 12-4



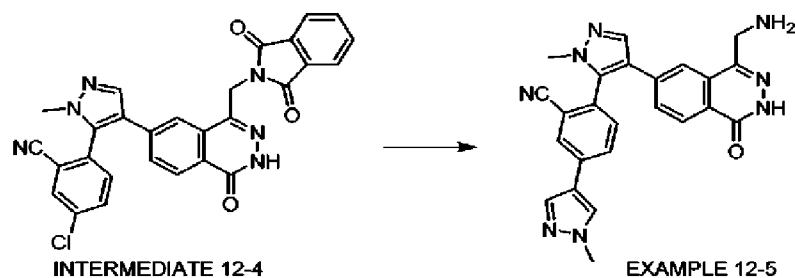
[0540] **Step 1:** A mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)-5-chloro-benzonitrile, Intermediate A-10 (300 mg, 1.01 mmol, 1.00 *eq.*), 2-[[4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione, Intermediate J (523 mg, 1.21 mmol, 1.20 *eq.*), *ditert*-butyl(cyclopentyl)phosphane-dichloropalladium iron (66 mg, 0.101 mmol, 0.10 *eq.*), sodium bicarbonate (170 mg, 2.02 mmol, 79 μL, 2.00 *eq.*) in 1,4-dioxane (10 mL) and water (2 mL) was degassed and purged with nitrogen 3 times then stirred at 80°C for 2 hours. After such time the reaction mixture was quenched by the addition of water (30 mL) at 20 °C then extracted with dichloromethane (30 mL × 2). The combined

organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 5-chloro-2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]benzonitrile, Intermediate 12-4 (300 mg, crude) as brown liquid which used into the next step without further purification. LCMS $[M+1]^+ = 521.1$

[0541] **Step 2:** A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole (39 mg, 0.184 mmol, 1.20 *eq.*), 5-chloro-2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]benzonitrile (80 mg, 0.153 mmol, 1.00 *eq.*), Xphos precatalyst G2 (36 mg, 0.046 mmol, 0.30 *eq.*) and potassium phosphate (65 mg, 0.307 mmol, 2.00 *eq.*) in 1,4-dioxane (4 mL) and water (0.4 mL) was degassed and purged with nitrogen 3 times then stirred at 110 °C for 1 hour. After such time the reaction was cooled to room temperature, diluted with dichloromethane (20 mL), washed with water (5 mL $\times$ 2) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-5-isothiazol-4-yl-benzonitrile (66 mg, crude) as a brown oil which used into the next step without further purification. LCMS $[M+1]^+ = 570.1$.

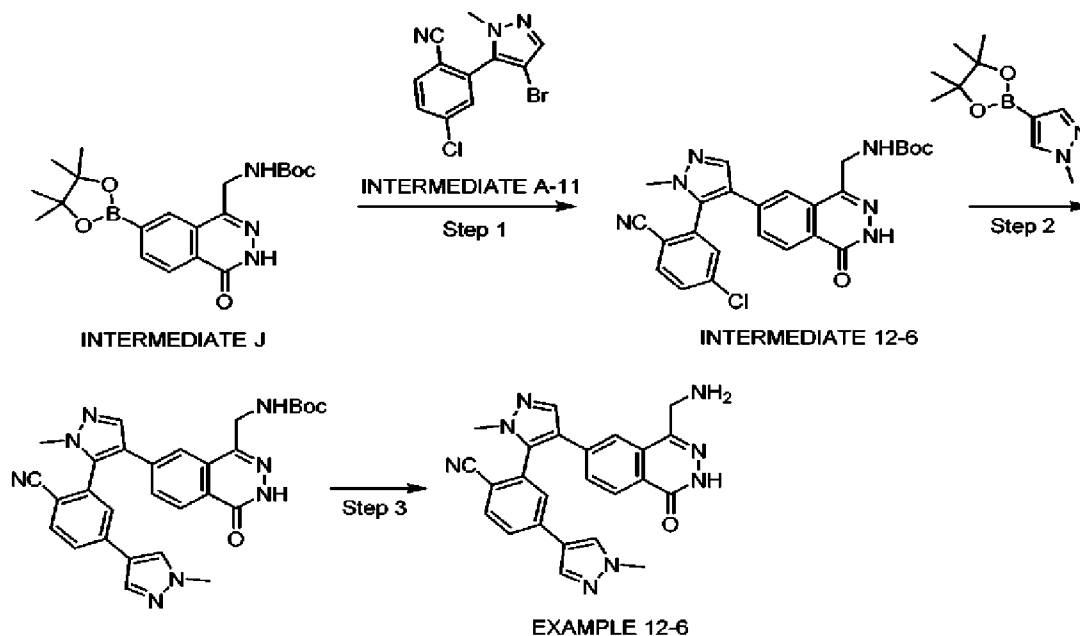
[0542] **Step 3:** To a solution of 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-5-isothiazol-4-yl-benzonitrile (60 mg, 0.105 mmol, 1.00 *eq.*) in 1,4-dioxane (5 mL) was added hydrazine hydrate (53 mg, 1.05 mmol, 51 μ L, 10 *eq.*). The mixture was stirred at 20 °C for 15 hours then concentrated under reduced pressure. The residue was purified by prep-HPLC (YMC-Actus Triart C18 150 $\times$ 30 mm $\times$ 5 μ m; mobile phase: [water (0.1%TFA)-ACN]; B%: 17%-43%, 11 min) to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-5-isothiazol-4-yl-benzonitrile, Example 12-4 (6 mg, 14% yield) as a white solid. LCMS $[M+1]^+ = 440.0$; ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.87 (s, 1H), 9.69 (s, 1H), 9.27 (s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 8.37 (br d, *J* = 2.0 Hz, 2H), 8.40 - 8.24 (m, 4H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.45 (dd, *J* = 1.6, 8.0 Hz, 1H), 4.39 - 4.26 (m, 2H), 3.78 (s, 3H).

EXAMPLE 12-5



[0543] Example 12-5, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-5-(1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl)benzonitrile was prepared from 5-chloro-2-[4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]benzonitrile, Intermediate 12-4 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole following the procedure described for the preparation of Example 12-4, steps 2 and 3 as a white solid (6 mg, 13 μ mol, 25% yield). LCMS $[M+1]^+ = 437.2$. ^1H NMR (400 MHz, CD_3OD) $\delta = 8.24$ (s, 1 H), 8.19 (s, 1 H), 8.16 (d, $J = 1.6$ Hz, 1 H), 8.12 (s, 1 H), 8.09 - 8.04 (m, 1 H), 8.01 (s, 1 H), 7.72 - 7.64 (m, 3 H), 3.96 (s, 3 H), 3.88 (s, 2 H), 3.83 (s, 3 H).

EXAMPLE 12-6



[0544] **Step 1:** To a solution of 2-(4-bromo-2-methyl-pyrazol-3-yl)-4-chloro-benzonitrile, Intermediate A-11 (160 mg, 0.539 mmol, 1.00 *eq.*), sodium bicarbonate (91 mg, 1.08 mmol,

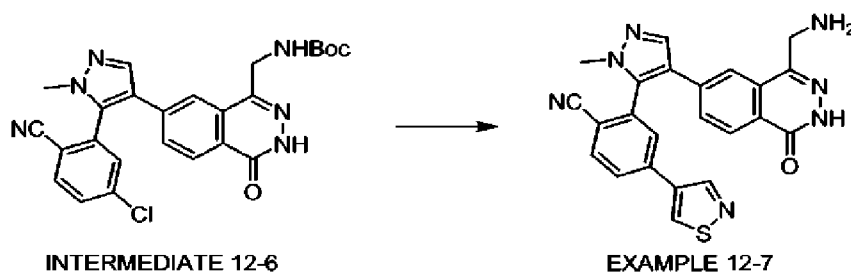
41.9 μL , 2.00 *eq.*) and *tert*-butyl-*N*-[[4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate J (281 mg, 0.701 mmol, 1.30 *eq.*) in 1,4-dioxane (5 mL) and water (1 mL) was added *di**tert*-butyl(cyclopentyl)phosphane-dichloropalladium iron (35 mg, 54 μmol , 0.10 *eq.*) and the mixture was stirred at 80 °C for 2 hours under nitrogen. After such time the reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic phase was separated, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash silica gel chromatography (50 to 100% petroleum ether: ethyl acetate gradient) to give *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate 12-6 (160 mg, 0.313 mmol, 58% yield) as a gray solid. LCMS $[\text{M}+1]^+ = 491.2$.

[0545] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (50 mg, 0.102 mmol, 1.00 *eq.*), potassium carbonate (42 mg, 0.305 mmol, 3.00 *eq.*) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (42 mg, 0.204 mmol, 2.00 *eq.*) in 1,4-dioxane (1.0 mL) and water (0.1 mL) was added *di**tert*-butyl(cyclopentyl)phosphane dichloropalladium iron (13 mg, 20.4 μmol , 0.20 *eq.*) and the mixture was stirred at 80 °C for 3 hours under nitrogen. After such time the reaction was cooled to 10°C and the salt was removed by filtration and the filtrate concentrated. The residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate 1: 1.5) to give *tert*-butyl *N*-[[7-[5-[2-cyano-5-(1-methylpyrazol-4-yl)phenyl]-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (40 mg, 64 μmol , 63% yield) as a white solid. LCMS $[\text{M}+1]^+ = 537.3$.

[0546] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[5-[2-cyano-5-(1-methylpyrazol-4-yl)phenyl]-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (37 mg, 63 μmol , 1.00 *eq.*) in methanol (2 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4 M, 2 mL) and the mixture was stirred at 25 °C for 2 hours. After such time the reaction mixture was concentrated and the residue was purified by prep-HPLC (Phenomenex Synergi C18 150 $\times$ 30 mm $\times$ 4 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 15%-35%, 9 min) to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-4-(1-methylpyrazol-4-yl)benzonitrile, Example 12-6 (7 mg, 16 μmol , 23% yield) as a white solid. LCMS $[\text{M}+1]^+ = 437.2$; ^1H NMR (400 MHz, CD_3OD) δ = 8.26 (s, 1H), 8.21 - 8.13 (m, 2H),

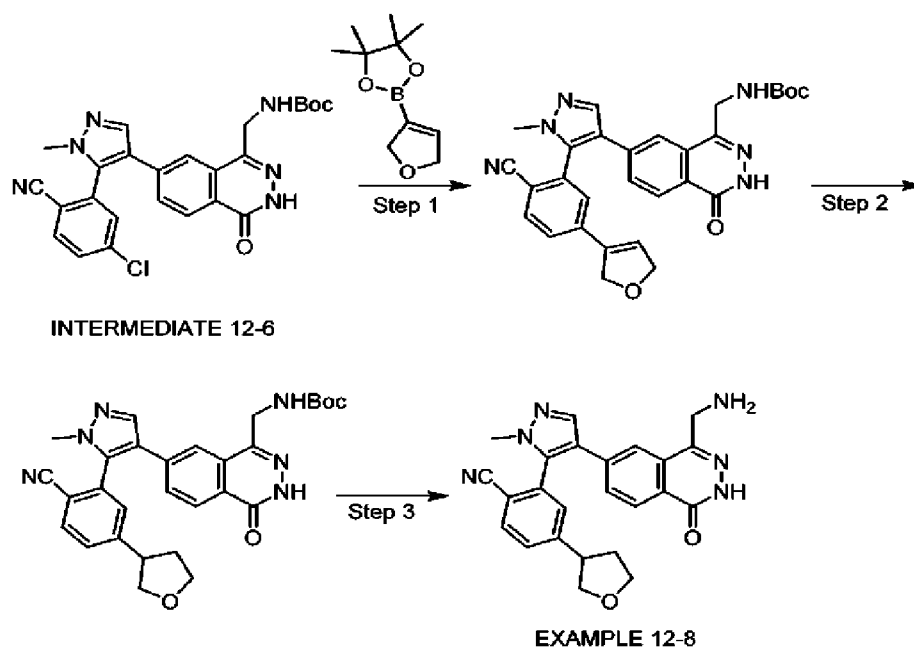
8.09 - 8.04 (m, 1H), 8.01 - 7.94 (m, 2H), 7.92 - 7.87 (m, 1H), 7.74 (d, $J = 1.2$ Hz, 1H), 7.58-7.55 (m, 1H), 4.38 (s, 2H), 3.96 (s, 3H), 3.85 (s, 3H).

EXAMPLE 12-7



[0547] Example 12-7, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-(isothiazol-4-yl)benzonitrile was prepared from *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate 12-6 and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole following the procedure described for the preparation of Example 12-6, steps 2 and 3 as a white solid (10 mg, 23 μ mol, 21% yield). LCMS $[M+1]^+ = 440.2$. ^1H NMR (400 MHz, CD_3OD) $\delta = 9.43$ (s, 1H), 9.05 (s, 1H), 8.21 - 8.14 (m, 4H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 1.2$ Hz, 1H), 7.58-7.56 (m, 1H), 4.46 - 4.33 (m, 2H), 3.87 (s, 3H).

EXAMPLE 12-8

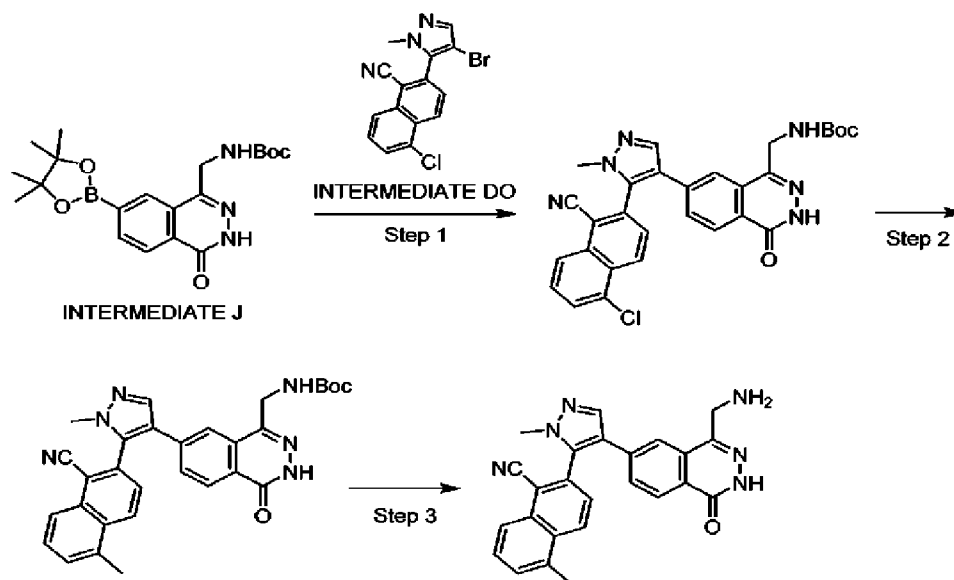


[0548] **Step 1:** To a solution of *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate 12-6 (100 mg, 0.204 mmol, 1.00 *eq.*), potassium carbonate (56 mg, 0.407 mmol, 2.00 *eq.*) and 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80 mg, 0.407 mmol, 2.00 *eq.*) in 1,4-dioxane (5 mL) and water (1 mL) was added *di**tert*-butyl(cyclopentyl)phosphanedichloropalladium iron (26.6 mg, 40.7 μ mol, 0.20 *eq.*). The mixture was stirred at 90 °C for 16 hours then cooled to 10 °C and the salts was removed by filtration. The filtrate was diluted with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 2) and the combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by prep-TLC (SiO₂, dichloromethane: methanol 20: 1) to give *tert*-butyl *N*-[[7-[5-[2-cyano-5-(2,5-dihydrofuran-3-yl)phenyl]-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (0.08 g, 0.114 mmol, 56% yield) as a gray solid. LCMS $[M+1]^+ = 525.3$.

[0549] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-[2-cyano-5-(2,5-dihydrofuran-3-yl)phenyl]-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (80 mg, 0.114 mmol, 1.00 *eq.*) in methanol (20 mL) was added palladium on activated carbon (6.6 mg, 11 μ mol, 10% Pd, 0.10 *eq.*) and the mixture was vigorously stirred at 25°C for 2 hours. After such time the mixture was filtered and the filtrate was concentrated to give *tert*-butyl *N*-[[7-[5-(2-cyano-5-THF-3-yl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (75 mg, 105 μ mol, 92% yield) as a white solid which used directly for the next step without further purification. LCMS $[M+1]^+ = 527.3$

[0550] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[5-(2-cyano-5-THF-3-yl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (74.0 mg, 105 μ mol, 1.00 *eq.*) in dichloromethane (2 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4.00 M, 0.26 mL, 10.0 *eq.*). The mixture was stirred at 25 °C for 1 hr then concentrated under reduced pressure and the residue purified by prep-HPLC (Welch Xtimate C18 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 12%-42%, 10 min) to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-4-THF-3-yl-benzonitrile, Example 12-8 (6 mg, 13 μ mol, 12% yield) as a white solid. LCMS $[M+1]^+ = 427.3$; ¹H NMR (400MHz, DMSO) δ = 12.37 (s, 1H), 8.17 (d, *J* = 0.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.70 - 7.64 (m, 3H), 7.47 (d, *J* = 1.2 Hz, 1H), 4.05 - 3.84 (m, 3H), 3.79 - 3.72 (m, 1H), 3.70 (s, 3H), 3.65 - 3.48 (m, 5H), 2.39 - 2.26 (m, 1H), 2.01 - 1.87 (m, 1H).

EXAMPLE 12-9

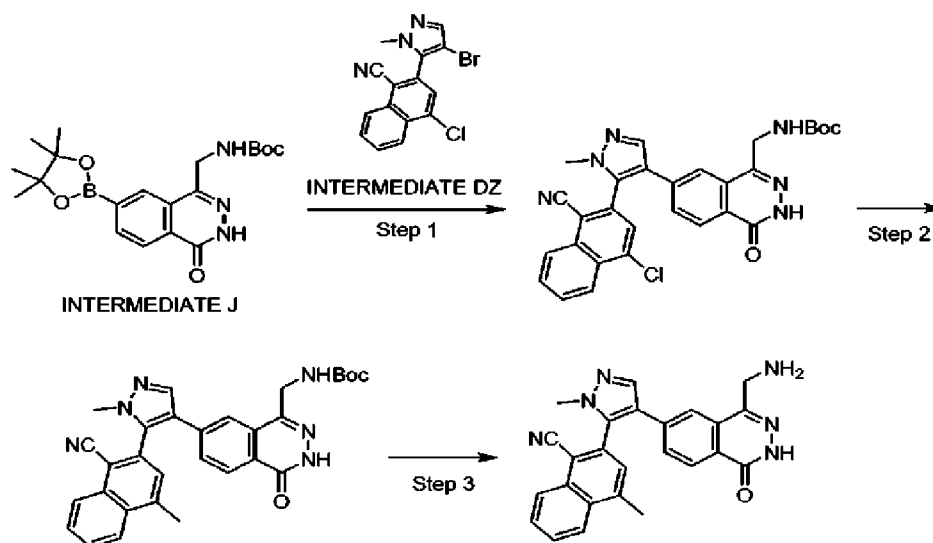


[0551] **Step 1:** A mixture of 2-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-1-naphthonitrile, Intermediate DO, (130 mg, 0.375 mmol, 1.00 *eq.*), *tert*-butyl *N*-[[4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-phthalazin-1-yl]methyl]carbamate, Intermediate J (181 mg, 0.45 mmol, 1.20 *eq.*), Pd(dtbpf)Cl₂ (24 mg, 38 μmol, 0.10 *eq.*), sodium carbonate (80 mg, 0.75 mmol, 2.00 *eq.*) in the mixed solvents dioxane (5 mL) and water (1 mL) was degassed with nitrogen and stirred at 80 °C for 1 hour under nitrogen atmosphere. After such time the mixture was concentrated and the residue was purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 20: 1) to give *tert*-butyl *N*-[[7-[5-(5-chloro-1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (120 mg, 0.222 mmol, 59% yield) as a white solid. LCMS [M+1]⁺ = 541.1.

[0552] **Step 2:** A mixture of *tert*-butyl *N*-[[7-[5-(5-chloro-1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (70 mg, 129 μmol, 1.00 *eq.*), methylboronic acid (23 mg, 0.388 mmol, 3.00 *eq.*), Pd(dtbpf)Cl₂ (8.4 mg, 12 μmol, 0.10 *eq.*), potassium carbonate (36 mg, 259 μmol, 2.00 *eq.*) in dioxane (2 mL) was degassed and purged with nitrogen and stirred at 100 °C for 1 hour under nitrogen atmosphere. The mixture was concentrated and purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 20: 1) to give *tert*-butyl *N*-[[7-[5-(1-cyano-5-methyl-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (50 mg, 96 μmol, 74% yield) as a white solid. LCMS [M+1]⁺ = 521.5.

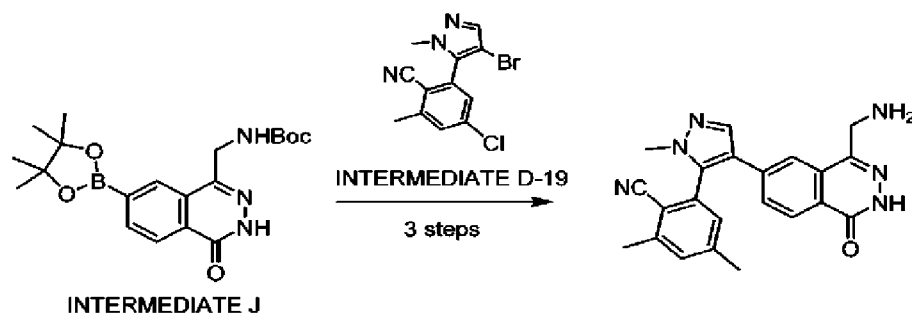
[0553] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[5-(1-cyano-5-methyl-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (50 mg, 96 μ mol, 1.00 *eq.*) in dichloromethane (1.5 mL) was added trifluoroacetic acid (417 μ L) and the mixture stirred at 25 °C for 0.5 hour. After such time the mixture was concentrated and the residue was purified by prep-HPLC (Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 17%-37%, 7 min) to give 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-1-naphthonitrile, Example 12-9 (21 mg, 45 μ mol, 47% yield, HCl) as a white solid. LCMS $[M+1]^+ = 421.1$; ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.83 (s, 1H), 8.59 (dd, *J* = 0.8, 8.8 Hz, 1H), 8.45 (br s, 3H), 8.35 (s, 1H), 8.05 - 7.96 (m, 2H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 - 7.74 (m, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.31 (dd, *J* = 1.6, 8.4 Hz, 1H), 4.44 - 4.17 (m, 2H), 3.77 (s, 3H), 2.79 (s, 3H).

EXAMPLE 12-10



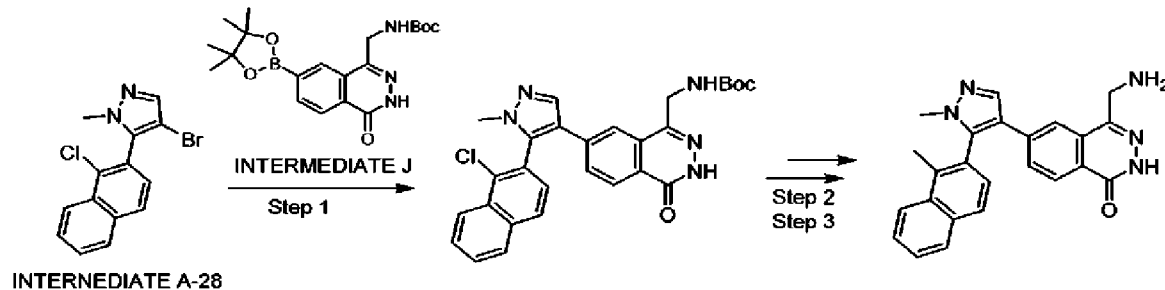
[0554] Example 12-10, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-methyl-1-naphthonitrile was prepared from Intermediate J (346 mg, 0.863 mmol, 1.30 *eq.*), and Intermediate DZ (230 mg, 0.664 μ mol, 1.00 *eq.*), according to the procedure described for the synthesis of Example 12-9 as a yellow solid (20 mg, 0.042 mmol, final step 55% yield). LCMS $[M+1]^+ = 421.1$; ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.83 (s, 1H), 8.55 - 8.43 (m, 3H), 8.36 (s, 1H), 8.36 - 8.32 (m, 1H), 8.18 - 8.12 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.93 - 7.86 (m, 3H), 7.75 (d, *J* = 0.8 Hz, 1H), 7.37 (dd, *J* = 1.6, 8.4 Hz, 1H), 4.45 - 4.11 (m, 2H), 3.78 (s, 3H), 2.86 (s, 3H).

EXAMPLE 12-11



[0555] 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4,6-dimethylbenzonitrile, Example 12-11 was prepared using the same method as Example 12-9 starting from Intermediate DO for Intermediate D-19, as a white solid (7.6 mg, 0.015 mmol, 37% yield). LCMS $[M+1]^+ = 385.2$; ^1H NMR (400 MHz, DMSO- d_6) δ = 12.89 - 12.85 (m, 1H), 8.36 (br s, 3H), 8.28 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.52 (s, 1H), 7.49 (dd, J = 1.6, 8.4 Hz, 1H), 7.41 (s, 1H), 4.35 - 4.11 (m, 2H), 3.71 (s, 3H), 2.52 - 2.51 (m, 3H), 2.44 (s, 3H).

EXAMPLE 12-12



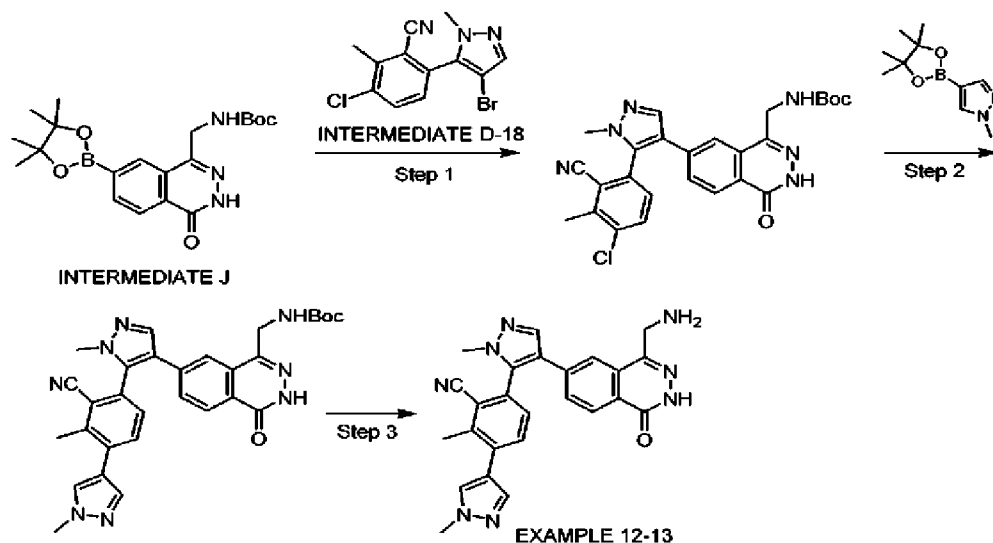
[0556] **Step 1:** A mixture of 4-bromo-5-(1-chloro-2-naphthyl)-1-methyl-pyrazole (1.20 g, 3.73 mmol, 1.00 eq.), *tert*-butyl *N*-[[4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-phthalazin-1-yl]methyl]carbamate (1.50 g, 3.73 mmol, 1.00 eq.), sodium bicarbonate (627 mg, 7.46 mmol, 2.00 eq.) and *ditert*-butyl(cyclopentyl)phosphane-dichloropalladium;iron (243 mg, 0.373 mmol, 0.10 eq.) in dioxane (10 mL) and water (2 mL) was degassed and purged with nitrogen 3 times, and stirred at 80 °C for 0.5 hour. The reaction mixture was then filtered and concentrated and the residue was diluted with water (30 mL) and extracted with ethyl acetate (30 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate = 10: 1 to 0: 1) to give *tert*-butyl *N*-[[7-[5-(1-chloro-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-

3*H*-phthalazin-1-yl)methyl]carbamate (1.20 g, 2.33 mmol, 62% yield) as a white solid. LCMS $[M+1]^+ = 516.1$; ^1H NMR (400 MHz, CDCl_3) $\delta = 10.08$ (s, 1H), 8.41 (d, $J = 8.0$ Hz, 1H), 8.18 - 8.10 (m, 1H), 8.04 (s, 1H), 7.96 (dd, $J = 8.4$, 16.0 Hz, 2H), 7.84 - 7.77 (m, 1H), 7.76 - 7.66 (m, 2H), 7.47 - 7.39 (m, 1H), 7.36 (d, $J = 8.8$ Hz, 1H), 5.27 - 5.15 (m, 1H), 4.46 - 4.38 (m, 1H), 4.33 - 4.26 (m, 1H), 3.77 (s, 3H), 1.49 (s, 9H).

[0557] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(1-chloro-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl)methyl]carbamate (100 mg, 0.194 mmol, 1.00 *eq.*) in toluene (2 mL) was added potassium phosphate (123 mg, 0.581 mmol, 3.00 *eq.*), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (292 mg, 1.16 mmol, 50% purity, 6.00 *eq.*) and SPhos Pd G2 (15 mg, 0.194 mmol, 0.10 *eq.*) and the mixture was stirred at 100 °C for 10 hours under nitrogen atmosphere. After such time the mixture was filtered, diluted with water (5 mL) and extracted with ethyl acetate (5 mL) and the organic layer dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *tert*-butyl *N*-[[7-[1-methyl-5-(1-methyl-2-naphthyl)pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl)methyl]carbamate (150 mg, crude) as a yellow solid. LCMS $[M+1]^+ = 496.5$.

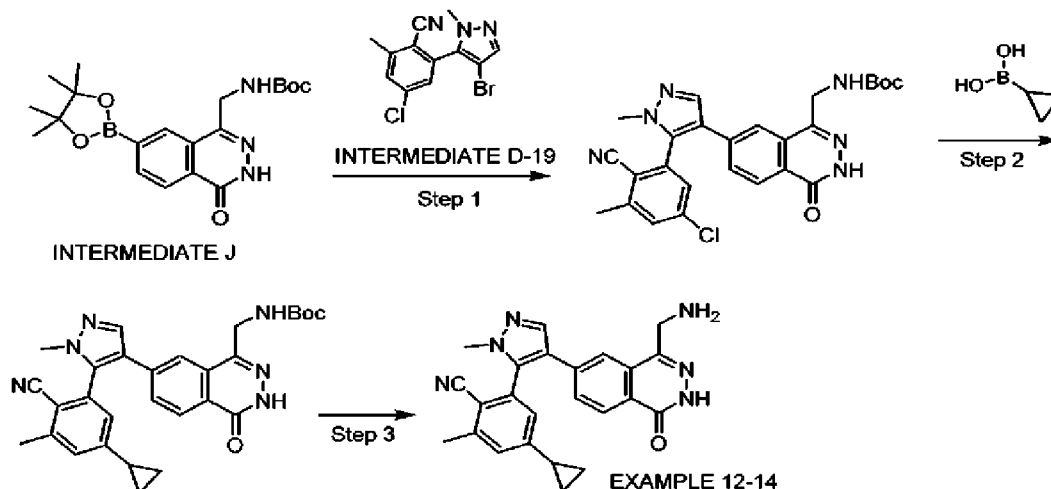
[0558] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[1-methyl-5-(1-methyl-2-naphthyl)pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl)methyl]carbamate (150 mg, 0.303 mmol, 1.00 *eq.*) in the dichloromethane (1 mL) was added trifluoroacetic acid (462 mg, 4.05 mmol, 0.30 mL, 13.4 *eq.*). The mixture was then stirred at 25 °C for 0.5 hour then concentrated and the residue purified by prep-HPLC (Phenomenex Synergi C18 150 × 30 mm × 4 μm ; mobile phase: [water (0.1% TFA)-ACN]; B%: 23%-43%, 10 min) to give 4-(aminomethyl)-6-[1-methyl-5-(1-methyl-2-naphthyl)pyrazol-4-yl]-2*H*-phthalazin-1-one (16 mg, 0.038 mmol, 13% yield) as an off-white solid. LCMS $[M+1]^+ = 396.1$; ^1H NMR (500 MHz, MeOD) $\delta = 8.23$ - 8.21 (m, 1H), 8.19 - 8.13 (m, 2H), 8.03 - 7.96 (m, 2H), 7.73 - 7.69 (m, 1H), 7.68 - 7.64 (m, 2H), 7.60 - 7.58 (m, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 4.14 (d, $J = 13.5$ Hz, 1H), 3.98 (d, $J = 13.0$ Hz, 1H), 3.70 (s, 3H), 2.43 (s, 3H).

EXAMPLE 12-13



[0559] Example 12-13, 6-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-2-methyl-3-(1-methyl-1H-pyrazol-4-yl)benzonitrile was prepared as a white solid (10 mg, 0.018 mmol, 33% yield), starting with Intermediate J and Intermediate D-18 following the same procedure as described for Example 12-6. LCMS $[M+1]^+ = 451.2$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) $\delta = 12.86$ (s, 1H), 8.33 (br s, 3H), 8.27 (s, 1H), 8.16 (s, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.86 (d, $J = 0.5$ Hz, 1H), 7.78 (d, $J = 1.5$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.48 (dd, $J = 1.5, 8.5$ Hz, 1H), 4.31 (br t, $J = 6.0$ Hz, 2H), 3.93 (s, 3H), 3.74 (s, 3H), 2.62 (s, 3H).

EXAMPLE 12-14



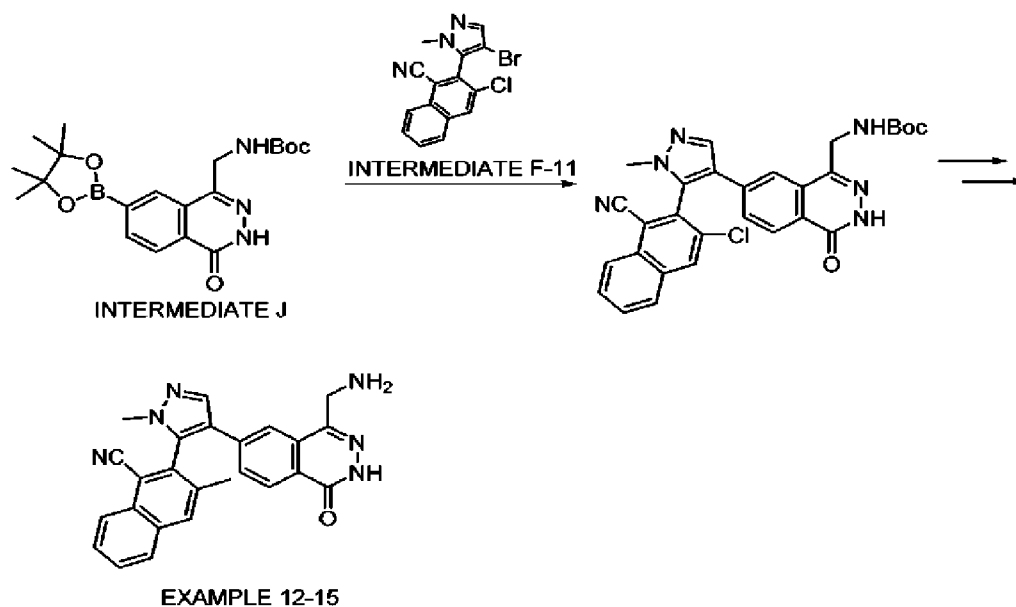
[0560] **Step 1:** A mixture of Intermediate J (350 mg, 0.872 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)-4-chloro-6-methyl-benzonitrile, intermediate D-19 (271 mg, 0.872 mmol, 1.00 *eq.*), sodium bicarbonate (220 mg, 2.62 mmol, 3.00 *eq.*) and *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (57 mg, 0.087 mmol, 0.10 *eq.*) in dioxane (3 mL) and water (0.6 mL) was degassed and purged with nitrogen 3 times and stirred at 80 °C for 1 hour. The mixture was then concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol = 10: 1) to give *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-3-methyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (135 mg, 0.174 mmol, 20% yield) as a yellow solid. LCMS [M+1]⁺ = 505.2.

[0561] **Step 2:** A mixture of *tert*-butyl *N*-[[7-[5-(5-chloro-2-cyano-3-methyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (35 mg, 0.069 mmol, 1.00 *eq.*), cyclopropylboronic acid (24 mg, 0.277 mmol, 4.00 *eq.*), tricyclohexyl-phosphine (2 mg, 0.007 mmol, 2.3 μL, 0.10 *eq.*), Pd₂(dba)₃ (6.4 mg, 0.007 mmol, 0.10 *eq.*) and potassium phosphate (44 mg, 0.208 mmol, 3.00 *eq.*) in dioxane (2 mL) was degassed and purged with nitrogen 3 times, and stirred at 100 °C for 12 hours. The mixture was then concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol = 10: 1) to give *tert*-butyl *N*-[[7-[5-(2-cyano-5-cyclopropyl-3-methyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (23 mg, 0.038 mmol, 54% yield) as a yellow solid. LCMS [M+1]⁺ = 511.3.

[0562] **Step 3:** A mixture of *tert*-butyl *N*-[[7-[5-(2-cyano-5-cyclopropyl-3-methyl-phenyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (18 mg, 0.035 mmol, 1.00 *eq.*) in trifluoroacetic acid (0.5 mL) and dichloromethane (1.5 mL) was purged with nitrogen 3 times, and stirred at 15 °C for 1 hour. The mixture was then concentrated and the residue purified by prep-HPLC (Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% trifluoroacetic acid)-ACN]; B%: 15%-45%, 10 min) to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-4-cyclopropyl-6-methyl-benzonitrile (11 mg, 0.021 mmol, 61% yield) as a white solid. LCMS [M+1]⁺ = 411.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.88 (s, 1H), 8.37 (br s, 3H), 8.28 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.46 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.37 (s, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 4.29 (br s, 2H), 3.71 (s, 3H), 3.34 - 3.34 (m, 3H), 2.10 - 1.98 (m, 1H), 1.10 (dd, *J* = 2.8, 8.4 Hz, 2H), 0.95 - 0.80 (m, 2H); ¹H NMR (400 MHz, CD₃OD) δ = 8.20 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.33 (s, 1H), 7.22 (d, *J* = 1.6

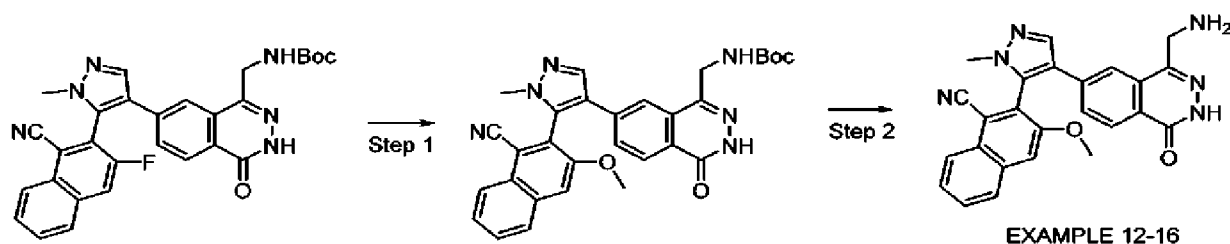
Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 2.53 (s, 3H), 2.09 - 2.01 (m, 1H), 1.18 - 1.11 (m, 2H), 0.92 - 0.79 (m, 2H).

EXAMPLE 12-15



[0563] Example 12-15, 2-[[4-[[4-(aminomethyl)-1-oxo-2H-phthalazin-6-yl]-2-methylpyrazol-3-yl]-3-methyl-naphthalen-1-yl]carbonitrile was prepared as a yellow gum starting from Intermediate F-11 and Intermediate J according to the same method as described for Example 12-9 (2.6 mg, 0.006 mmol, 3% yield over 3 steps). LCMS $[M+H]^+ = 421.2$; ^1H NMR (400 MHz, DMSO- d_6) $\delta = 12.80$ (s, 1H), 8.43 (d, $J = 8.0$ Hz, 2H), 8.19 - 8.15 (m, 1H), 8.13 - 8.10 (m, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 7.86 (s, 1H), 7.85 - 7.79 (m, 2H), 7.26 (d, $J = 8.4$ Hz, 1H), 4.36 - 4.18 (m, 2H), 4.09 (s, 2H), 3.66 (s, 3H), 2.21 (s, 3H).

EXAMPLE 12-16

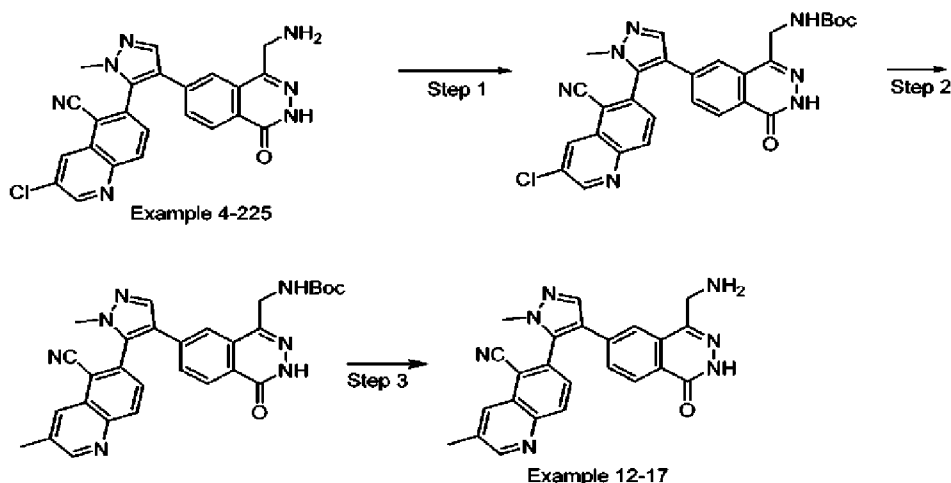


[0564] **Step 1:** To a solution of *tert*-butyl *N*-[[7-[5-(1-cyano-3-fluoro-2-naphthyl)-1-methylpyrazol-4-yl]-4-oxo-3H-phthalazin-1-yl]methyl]carbamate (100 mg, 0.19 mmol, 1.00 *eq.*) in

methyl alcohol (3 mL) was added sodium methoxide (309 mg, 5.72 mmol, 30.0 *eq.*) and the mixture was stirred at 110 °C for 5 hours. After such time the mixture was diluted with ethyl acetate (20 mL) and washed with brine (20 mL × 3), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol = 5%) to give *tert*-butyl *N*-[[7-[5-(1-cyano-3-methoxy-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (30 mg, 0.056 mmol, 29% yield) as a yellow solid. LCMS [M+1]⁺ = 537.2.

[0565] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(1-cyano-3-methoxy-2-naphthyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (30 mg, 0.056 mmol, 1.00 *eq.*) in dichloromethane (1.5 mL) was added trifluoroacetic acid (0.5 mL) and the mixture was stirred at 25 °C for 0.5 hour. The mixture was then concentrated and the residue was purified by prep-HPLC, purification method 4-6 to give 2-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-methoxy-naphthalene-1-carbonitrile (8.33 mg, 0.017 mmol, 31% yield, HCl) as a yellow solid. LCMS [M+1]⁺ = 437.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.81 (s, 1H), 8.51 (br s, 3H), 8.36 (s, 1H), 8.23 - 8.10 (m, 2H), 8.00 (br t, *J* = 8.0 Hz, 2H), 7.85 (s, 1H), 7.81 - 7.61 (m, 2H), 7.33 (br d, *J* = 8.4 Hz, 1H), 4.41 - 4.14 (m, 2H), 3.97 (s, 3H), 3.68 (s, 3H).

EXAMPLE 12-17



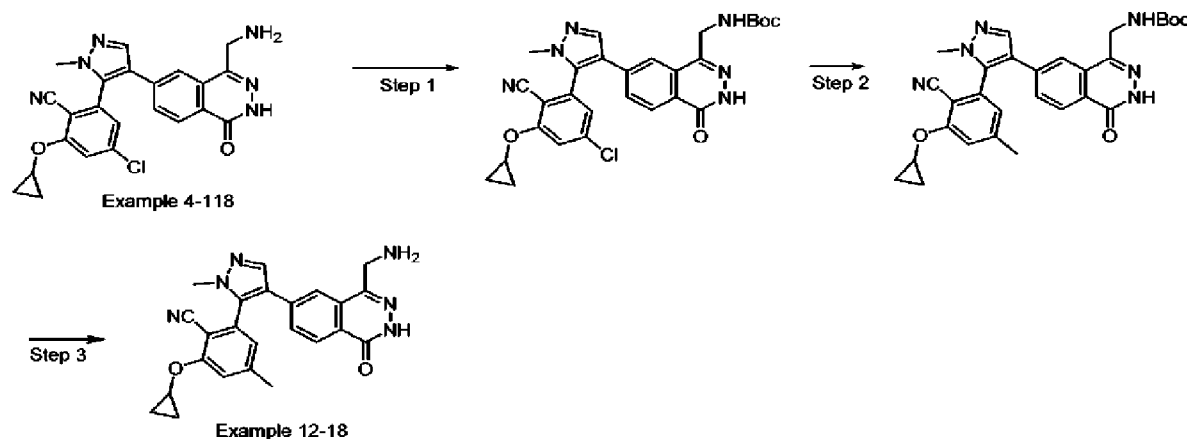
[0566] **Step 1:** To a solution of Example 4-225, 6-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-chloro-quinoline-5-carbonitrile (150 mg, 0.34 mmol, 1.00 *eq.*) in dichloromethane (10 mL) was added diisopropylethylamine (1.02 mmol, 0.18 mL, 3.00 *eq.*) and di-*tert*-butyl dicarbonate (111 mg, 0.51 mmol, 1.50 *eq.*) and the

mixture was stirred at 25 °C for 2 hours. The reaction mixture was then diluted with water (50 mL), extracted with ethyl acetate (50 mL × 3) and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, concentrated and the residue was purified by prep-TLC (SiO₂, petroleum ether: ethyl acetate 50%) to give *tert*-butyl *N*-[[7-[5-(3-chloro-5-cyano-6-quinolyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (130 mg, 0.24 mmol, 71 % yield) as a yellow solid. LCMS [M+1]⁺ = 542.1.

[0567] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(3-chloro-5-cyano-6-quinolyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (120 mg, 0.22 mmol, 1.00 *eq.*) in dioxane (5 mL) was added potassium carbonate (92 mg, 0.66 mmol, 3.00 *eq.*), *di**tert*-butyl(cyclopentyl)phosphane;dichloropalladium-iron (14 mg, 0.022 mmol, 0.10 *eq.*) and methylboronic acid (66 mg, 1.11 mmol, 5.00 *eq.*). The mixture was stirred at 100 °C for 2 hours and then the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, concentrated and the residue purified by prep-TLC (SiO₂, ethyl acetate) to give *tert*-butyl *N*-[[7-[5-(5-cyano-3-methyl-6-quinolyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (56 mg, 0.107 mmol, 49% yield) as a yellow solid. LCMS [M+1]⁺ = 522.3.

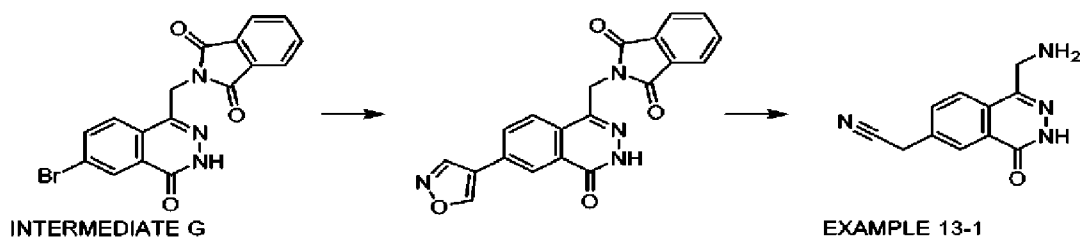
[0568] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[5-(5-cyano-3-methyl-6-quinolyl)-1-methyl-pyrazol-4-yl]-4-oxo-3*H*-phthalazin-1-yl]methyl]carbamate (66 mg, 0.127 mmol, 1.00 *eq.*) in dichloromethane (1 mL) was added trifluoroacetic acid (0.3 mL) and the mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was then concentrated and the residue purified by prep-HPLC (purification method 4-6) to give 6-[4-[4-(aminomethyl)-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-methyl-quinoline-5-carbonitrile (14 mg, 0.030 mmol, 24% yield, HCl) as a yellow solid. LCMS [M+1]⁺ = 422.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.83 (s, 1H), 9.08 (d, *J* = 2.0 Hz, 1H), 8.52 (br d, *J* = 8.0 Hz, 4H), 8.37 (s, 1H), 8.33 - 8.30 (m, 1H), 8.01 (d, *J* = 5.2 Hz, 1H), 7.99 (d, *J* = 5.2 Hz, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.34 (dd, *J* = 1.6, 8.4 Hz, 1H), 4.33 - 4.23 (m, 2H), 3.79 (s, 3H), 2.61 (s, 3H).

EXAMPLE 12-18



[0569] Example 12-18, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-6-cyclopropoxy-4-methylbenzonitrile, was prepared as a white solid starting from Example 4-118 according to the same method as described for Example 12-17 (11 mg, 0.022 mmol, 65% yield, 3% yield over 3 steps). LCMS $[M+1]^+ = 427.2$; ^1H NMR (400 MHz, DMSO- d_6) δ = 12.85 (s, 1H), 8.54 (br s, 3H), 8.28 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.58 (s, 1H), 7.51 (dd, J = 1.6, 8.4 Hz, 1H), 7.17 (s, 1H), 4.34 - 4.10 (m, 3H), 3.71 (s, 3H), 2.50 (br s, 3H), 0.94 - 0.85 (m, 2H), 0.84 - 0.71 (m, 2H); ^1H NMR (400 MHz, MeOD) δ = 8.20 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 7.78 (s, 1H), 7.56 (s, 1H), 7.52 (dd, J = 1.6, 8.4 Hz, 1H), 7.13 (s, 1H), 4.54 - 4.35 (m, 2H), 4.05 (tt, J = 2.8, 6.0 Hz, 1H), 3.79 (s, 3H), 2.55 (s, 3H), 0.92 (m, 2H), 0.86 - 0.73 (m, 2H).

EXAMPLE 13-1

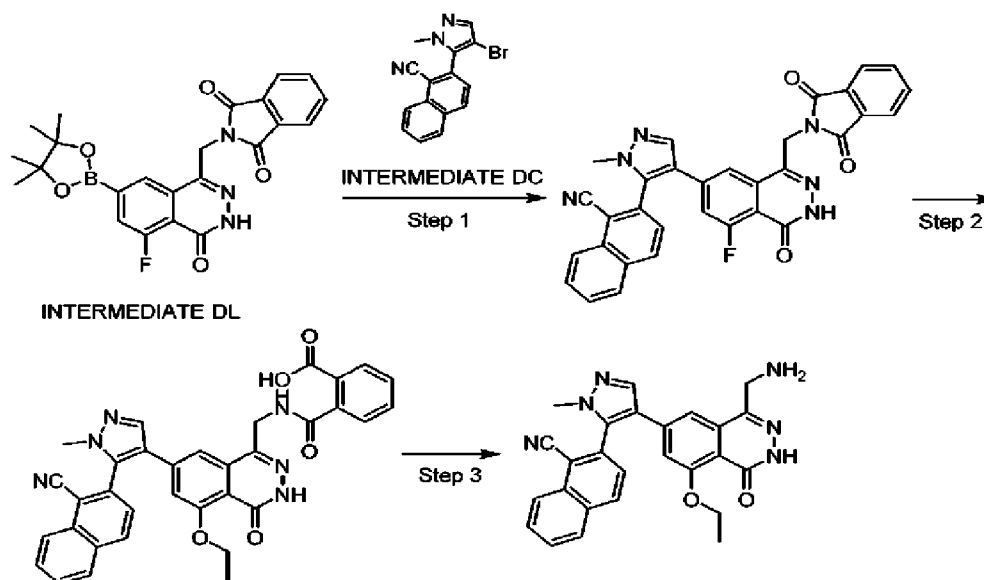


[0570] **Step 1:** A mixture of Intermediate G (1.00 g, 2.60 mmol, 1.00 *eq.*), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (609 mg, 3.12 mmol, 1.20 *eq.*), potassium fluoride (1.00 M, 7.81 mL, 3.00 *eq.*) and Pd(dppf)Cl₂ (170 mg, 0.26 mmol, 0.10 *eq.*) in DMSO (30 mL) was degassed and purged with nitrogen 3 times then stirred at 130 °C for 16 hours. After such time the reaction mixture was diluted with water (100 mL) and extracted

with ethyl acetate (30 mL $\times$ 3). The combined organic extracts were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 1/1 to 1/0, then methyl alcohol/ethyl acetate 1/10 followed by dichloromethane/methyl alcohol 10/1) to give 2-[(6-isoxazol-4-yl-4-oxo-3*H*-phthalazin-1-yl)methyl]isoindoline-1,3-dione (239 mg, 0.642 mmol, 25% yield) as a red solid. LCMS [$M+1$]⁺ = 373.1.

[0571] **Step 2:** To a solution of 2-[(6-isoxazol-4-yl-4-oxo-3*H*-phthalazin-1-yl)methyl]isoindoline-1,3-dione (200 mg, 0.537 mmol, 1.00 *eq.*) in ethyl alcohol (10 mL) was added hydrazine hydrate (0.053 mL, 1.07 mmol, 2.00 *eq.*) and the mixture stirred at 80 °C for 1 hour. After such time the pH of the cooled reaction mixture was adjusted to pH 1 with hydrochloric acid (1.00 M, 2.00 mL) and concentrated under reduced pressure. The residue diluted with hydrochloric acid (1.00 M, 40 mL) and extracted with ethyl acetate (30 mL $\times$ 3) and the aqueous phase was concentrated under reduced pressure. The residue was purified by prep-HPLC (Waters Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 0%-20%, 10 min) to give 2-[1-(aminomethyl)-4-oxo-3*H*-phthalazin-6-yl]acetonitrile, example 13-1 (32 mg, 0.145 mmol, 27% yield) as a white solid. LCMS [$M+1$]⁺ = 215.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.27 (d, *J* = 1.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.87 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.26 (s, 2H), 4.03 (s, 2H).

EXAMPLE 13-2



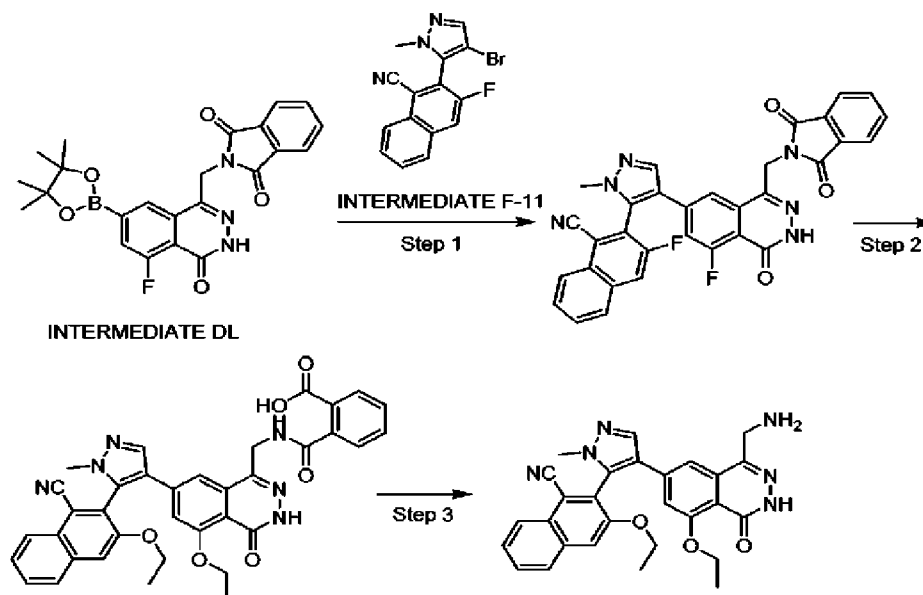
[0572] **Step 1:** To a mixture of 2-[[5-fluoro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione, Intermediate DL (100 mg, 0.223 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile, Intermediate DC (70 mg, 0.223 mmol, 1.00 *eq.*) and sodium bicarbonate (56 mg, 0.668 mmol, 26.0 μ L, 3.00 *eq.*) in dioxane (4 mL) and water (0.8 mL) was added *di*tert-butyl(cyclopentyl)phosphane;dichloropalladium-iron (14.5 mg, 0.022 mmol, 0.10 *eq.*) and the reaction mixture was degassed and purged with nitrogen and stirred at 80 °C for 1 hour. After such time the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (SiO₂, dichloromethane: methanol = 10: 1) to give 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-8-fluoro-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (50 mg, 0.074 mmol, 34% yield) as a white solid. LCMS [M+]⁺ = 555.2.

[0573] **Step 2:** To a mixture of 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-8-fluoro-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (30 mg, 0.054 mmol, 1.00 *eq.*) in ethyl alcohol (2 mL) was added sodium ethoxide (74 mg, 3.20 mmol, 76 μ L, 59 *eq.*) in one portion at 20 °C under nitrogen atmosphere. The mixture was stirred at 110 °C for 2 hours in a sealed tube then quenched with concentrated HCl (0.1 mL) to pH=5. The mixture was then concentrated under reduce pressure to give 2-[[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (20.0 mg, crude) as a white solid which used for the next step without further purification. LCMS [M+]⁺ = 599.1.

[0574] **Step 3:** To a mixture of 2-[[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (20 mg, crude) in ethyl alcohol (4 mL) was added hydrazine hydrate (334 μ mol, 16 μ L, 10.0 *eq.*) in one portion at 20 °C under nitrogen. Then the mixture was stirred at 70 °C for 12 hours and after such time the solvent was removed under reduce pressure and the residue dissolved in dimethylsulfoxide (2 mL) to which concentrated HCl (0.2 mL) was added to the reaction mixture to pH 6, and the resulting mixture was purified by Prep-HPLC (Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 17%-37%, 7 min) to give 2-[4-[4-(aminomethyl)-8-ethoxy-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (6 mg, 12 μ mol, 36% yield) as a yellow solid. LCMS [M+]⁺ = 451.4; ¹H NMR (400 MHz, CD₃OD) δ = 8.49 (d, *J* = 8.4 Hz, 1H), 8.25 - 8.19 (m, 3H), 7.91 - 7.82 (m, 2H),

7.80 (d, $J = 8.4$ Hz, 1H), 7.33 (s, 1H), 6.78 (d, $J = 1.2$ Hz, 1H), 4.46 - 4.19 (m, 2H), 3.86 (s, 3H), 3.68 - 3.38 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H).

EXAMPLE 13-3



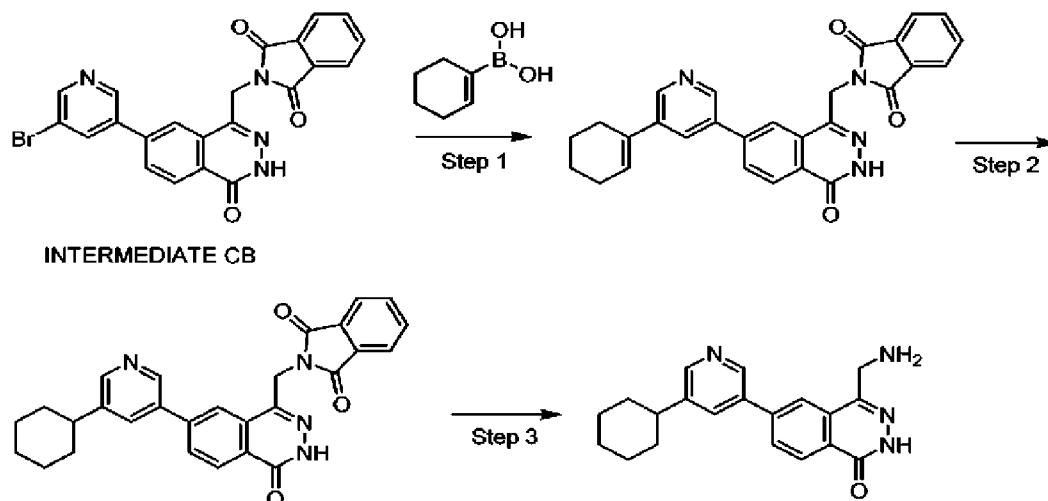
[0575] **Step 1:** To a mixture of 2-[[5-fluoro-4-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-phthalazin-1-yl]methyl]isoindoline-1,3-dione (61 mg, 0.136 mmol, 1.50 *eq*), 2-(4-bromo-2-methyl-pyrazol-3-yl)-3-fluoro-naphthalene-1-carbonitrile (30 mg, 0.090 mmol, 1.00 *eq*) and sodium bicarbonate (23 mg, 0.273 mmol, 3.00 *eq*) in dioxane (3.0 mL) and H₂O (0.6 mL) was added SPhos Pd G3 (7 mg, 0.009 mmol, 0.1 *eq*) then stirred at 80 °C for 1 hour under nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure and purified by prep-TLC (SiO₂, dichloromethane: methanol = 10: 1) to give 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-8-fluoro-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-fluoro-naphthalene-1-carbonitrile (10 mg, 0.005 mmol, 6% yield) as a white solid. LCMS $[M+1]^+ = 573.3$.

[0576] **Step 2:** To a mixture of 2-[4-[4-[(1,3-dioxoisindolin-2-yl)methyl]-8-fluoro-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-fluoro-naphthalene-1-carbonitrile (10 mg, 0.016 mmol) in ethanol (2.0 mL) was added freshly prepared sodium ethoxide (50 mg in 0.5 mL EtOH) in one portion at 20 °C under N₂ atmosphere. The mixture was stirred at 110 °C for 2 hours in a sealed tube. The reaction was then quenched with concentrated HCl then concentrated under reduce pressure to give 2-[[7-[5-(1-cyano-3-ethoxy-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3H-phthalazin-1-yl]methylcarbamoyl]benzoic acid (10 mg,

crude) as a white solid which used for the next step without further purification. LCMS $[M+1]^+ = 643.6$.

[0577] **Step 3:** To a mixture of 2-[[7-[5-(1-cyano-3-ethoxy-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (10 mg, 0.016 mmol, 1.00 *eq*) in ethanol (2.0 mL) was added hydrazine hydrate (0.155 mmol, 8 μ L, 10 *eq*.) in one portion at 20°C under N₂ atmosphere. The mixture was then stirred at 70 °C for 12 hours, concentrated and the residue dissolved in DMSO (2.0 mL) and the pH adjusted to pH 6 via the addition of concentrated HCl. The resulting mixture was then purified by prep-HPLC (Shim-pack C18 150 x 25 mm x 10 μ m; mobile phase: [water (0.1% TFA)-ACN]; B%: 10% - 40%, 10 min) to give 2-[4-[4-(aminomethyl)-8-ethoxy-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-ethoxy-naphthalene-1-carbonitrile (3 mg, 0.005 mmol, 31% yield) as a yellow solid. LCMS $[M+1]^+ = 495.4$; ¹H NMR (400 MHz, MeOD) δ = 8.25 (s, 1H), 8.10 (t, *J* = 8.0 Hz, 2H), 8.00 (s, 1H), 7.79 - 7.73 (m, 1H), 7.70 - 7.63 (m, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 6.77 (d, *J* = 0.8 Hz, 1H), 4.45 - 4.27 (m, 4H), 3.82 (s, 3H), 3.68 - 3.60 (m, 1H), 3.48 - 3.41 (m, 1H), 1.37 (s, 4H), 0.99 (t, *J* = 6.8 Hz, 3H).

EXAMPLE 14-1



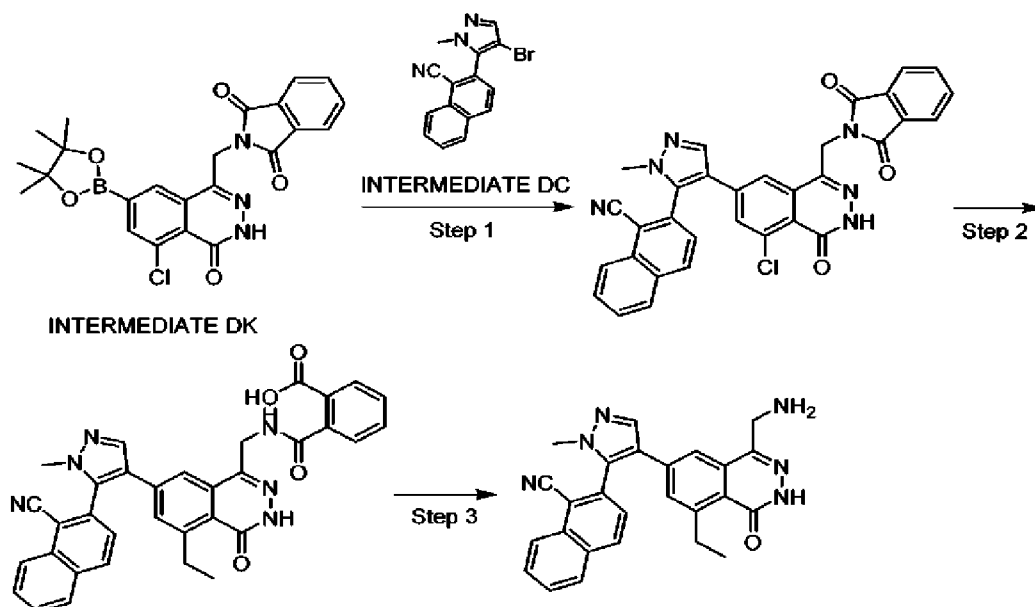
[0578] **Step 1:** A mixture of 2-[[7-(5-bromo-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione, Intermediate CB (300 mg, 0.650 mmol, 1.00 *eq*), cyclohexen-1-ylboronic acid (164 mg, 1.30 mmol, 2.00 *eq*), Pd(dppf)Cl₂ (48 mg, 65 μ mol, 0.10 *eq*), sodium bicarbonate (109 mg, 1.30 mmol, 51 μ L, 2.00 *eq*.) in dioxane (4 mL) and water (0.8 mL) was degassed and purged with nitrogen 3 times and stirred at 80 °C for 2

hours under nitrogen atmosphere. After such time the reaction mixture was concentrated and the residue was purified by column chromatography (SiO₂, petroleum ether: ethyl acetate 5: 1 to 0: 1) then by prep-HPLC (Phenomenex luna C18 150 x 25 mm x 10 µm; mobile phase: [water (0.1% TFA)-ACN]; B%: 34%-54%, 10 min) to give 2-[[7-[5-(cyclohexen-1-yl)-3-pyridyl]-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (20 mg, 43 µmol, 7% yield) as a yellow solid. LCMS [M+1]⁺ = 463.2.

[0579] **Step 2:** To a solution of 2-[[7-[5-(cyclohexen-1-yl)-3-pyridyl]-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (10 mg, 22 µmol, 1.00 *eq.*) in methyl alcohol (2 mL) was added 10% palladium on activated carbon (5 mg, 0.1 *eq.*) and the suspension was degassed and purged with hydrogen 3 times. The mixture was then stirred under hydrogen (15 Psi) at 25 °C for 2 hours. After such time the reaction mixture was filtered and concentrated under reduced pressure to give 2-[[7-(5-cyclohexyl-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (10 mg, crude) as a yellow solid which was used into next step directly without further purification. LCMS [M+1]⁺ = 465.3.

[0580] **Step 3:** To a solution of 2-[[7-(5-cyclohexyl-3-pyridyl)-4-oxo-3*H*-phthalazin-1-yl]methyl]isoindoline-1,3-dione (10 mg, 22 µmol, 1.00 *eq.*) in ethyl alcohol (1 mL) was added hydrazine hydrate (11 mg, 0.215 mmol, 11 µL, 10.0 *eq.*) and the reaction mixture stirred at 80 °C for 0.5 hour. After such time the reaction mixture was concentrated under reduced and purified by prep-HPLC (Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm; mobile phase: [water (0.1% TFA)-ACN]; B%: 15%-25%, 7 min) to give 4-(aminomethyl)-6-(5-cyclohexyl-3-pyridyl)-2*H*-phthalazin-1-one (3.6 mg, 8 µmol, 36% yield, TFA) as a yellow solid. LCMS [M+1]⁺ = 335.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.99 (s, 1H), 8.98 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 8.45 (br s, 3H), 8.41 - 8.37 (m, 1H), 8.33 - 8.29 (m, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.18 (t, *J* = 2.0 Hz, 1H), 4.63 (br d, *J* = 5.6 Hz, 2H), 2.71 - 2.65 (m, 1H), 1.92 - 1.81 (m, 4H), 1.79 - 1.71 (m, 1H), 1.66 - 1.51 (m, 2H), 1.48 - 1.36 (m, 2H), 1.34 - 1.23 (m, 1H).

EXAMPLE 15-1



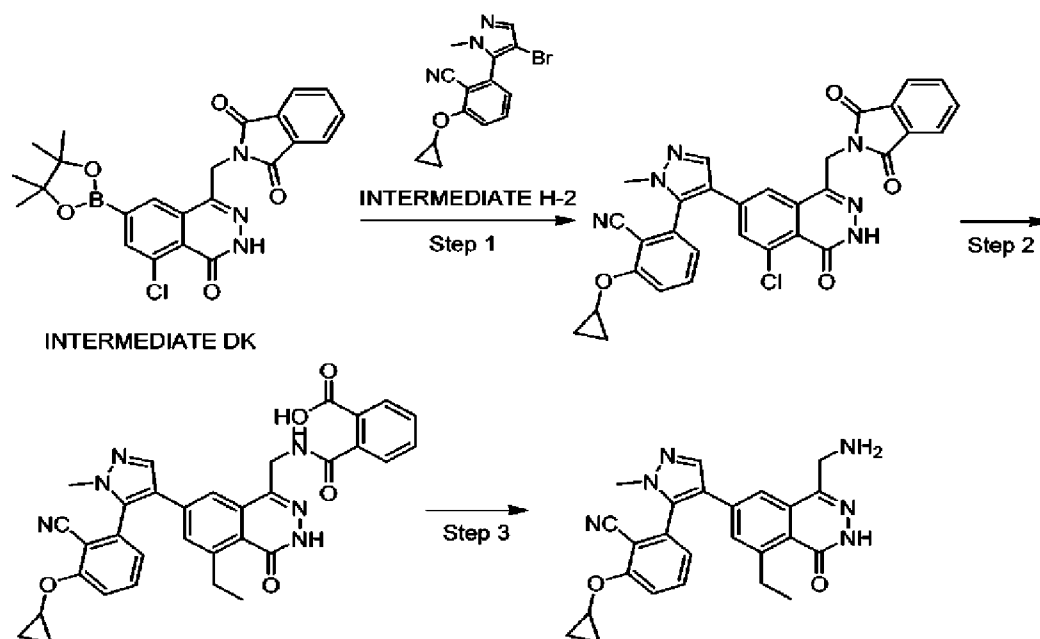
[0581] **Step 1:** A mixture of Intermediate DK (60 mg, 0.129 mmol, 1.00 *eq.*), 2-(4-bromo-2-methyl-pyrazol-3-yl)naphthalene-1-carbonitrile (40 mg, 0.129 mmol, 1.00 *eq.*), *tert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (8.4 mg, 0.012 mmol, 0.10 *eq.*), sodium bicarbonate (33 mg, 0.39 mmol, 3.00 *eq.*) in dioxane (3.0 mL) and water (0.5 mL) was degassed and purged with nitrogen 3 times, and then stirred at 80 °C for 1 hour under nitrogen atmosphere. The mixture was then concentrated and the residue purified by prep-TLC (SiO₂, dichloromethane: methyl alcohol 10: 1) to give 2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (40 mg, 0.064 mmol, 50% yield) as a yellow solid. LCMS [M+1]⁺ = 571.2.

[0582] **Step 2:** A mixture of 2-[4-[8-chloro-4-[(1,3-dioxoisindolin-2-yl)methyl]-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (40 mg, 0.070 mmol, 1.00 *eq.*), triethylborane (69 mg, 0.701 mmol, 0.101 mL, 10.0 *eq.*), Xantphos (4 mg, 0.007 mmol, 0.10 *eq.*), potassium carbonate (29 mg, 0.210 mmol, 3.00 *eq.*) in water (0.6 mL) and THF (3.0 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 80 °C in a sealed tube for 5 hours. The mixture was then concentrated under reduced pressure and the pH of the residue was adjusted to pH 7 by the addition of hydrochloric acid (1 M) aqueous solution then further concentrated to give 2-[[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethyl-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (100 mg, crude) as a

black solid, which was used into next step directly without further purification. LCMS $[M+1]^+ = 583.0$,

[0583] **Step 3:** A mixture of 2-[[7-[5-(1-cyano-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethyl-4-oxo-3*H*-phthalazin-1-yl]methylcarbamoyl]benzoic acid (100 mg, 0.172 mmol, 1.00 *eq.*), hydrazine hydrate (3.43 mmol, 0.17 mL, 20.0 *eq.*) in ethyl alcohol (5.0 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 80 °C for 18 hours. The mixture was then concentrated, and the residue acidified with hydrochloric acid (1 M) to pH 6, diluted with ethyl acetate (8 mL) and extracted with water (5 mL $\times$ 3). The aqueous layers were concentrated under reduced pressure and the residue was purified by prep-HPLC (Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.05% hydrochloric acid)-ACN]; B%: 18% - 38%, 7 min) to give 2-[4-[4-(aminomethyl)-8-ethyl-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]naphthalene-1-carbonitrile (13 mg, 0.027 mmol, 16% yield, HCl salt) as a yellow solid. LCMS $[M+1]^+ 435.3$; ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.61 (s, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 3H), 8.39 (s, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.93 - 7.81 (m, 3H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.01 (d, *J* = 1.2 Hz, 1H), 4.38 - 4.09 (m, 2H), 3.80 (s, 3H), 3.09 - 2.81 (m, 2H), 0.65 (t, *J* = 7.6 Hz, 3H).

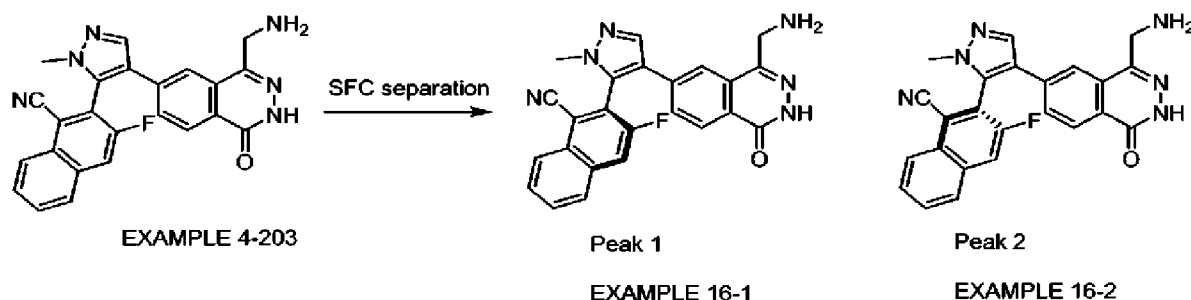
EXAMPLE 15-2



[0584] 2-[4-[4-(aminomethyl)-8-ethyl-1-oxo-1,2-dihydrophthalazin-6-yl]-1-methyl-1*H*-pyrazol-5-yl]-6-cyclopropoxybenzonitrile, Example 15-2 was prepared as a white solid (9 mg,

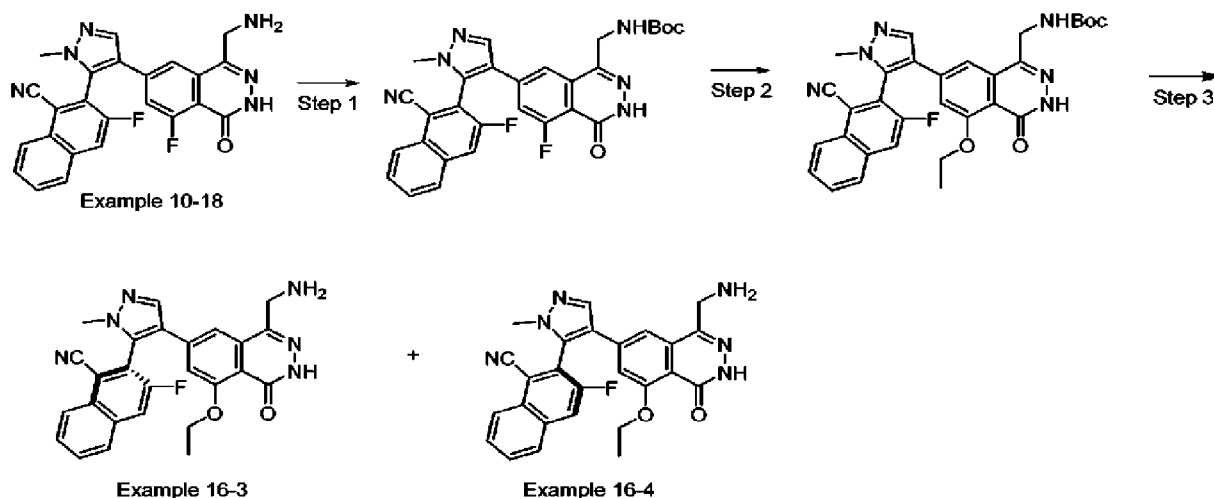
0.019 mmol, 12% yield, HCl salt) following the same 3 step procedure as for example 15-1 starting with Intermediate H-2. LCMS $[M+1]^+$ 441.3; ^1H NMR (400 MHz, DMSO- d_6) δ = 12.63 (s, 1H), 8.51 (br s, 3H), 8.32 (s, 1H), 7.98 - 7.88 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 1.2 Hz, 1H), 4.30 - 4.12 (m, 3H), 3.73 (s, 3H), 3.25 - 3.01 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H), 0.92 - 0.85 (m, 2H), 0.82 - 0.67 (m, 2H).

EXAMPLE 16-1 & 16-2



[0585] Example 4-203 (30 mg, 0.071 mmol) was separated by SFC (Daicel Chiralpak AD (250 mm $\times$ 30 mm, 10 μm); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ EtOH]; B%: 40%–40%, 4.9 min; 40 min) to provide Example 16-1 (6 mg, 0.014 mmol, 19% yield) as a white solid LCMS $[M+1]^+$ = 425.2; ^1H NMR (400 MHz, CD_3OD) δ = 8.20 - 8.15 (m, 1H), 8.13 - 8.03 (m, 4H), 7.76 - 7.67 (m, 2H), 7.59 (d, J = 1.2 Hz, 1H), 7.49 (dd, J = 1.6, 8.4 Hz, 1H), 3.85 - 3.79 (m, 1H), 3.76 (s, 3H), 3.75 - 3.70 (m, 1H) and Example 16-2 (6 mg, 0.014 mmol, 19% yield) as a white solid LCMS $[M+1]^+$ = 425.2; ^1H NMR (400 MHz, CD_3OD) δ = 8.18 (d, J = 10.0 Hz, 1H), 8.13 (s, 1H), 8.12 - 8.02 (m, 3H), 7.79 - 7.67 (m, 3H), 7.36 (dd, J = 1.2, 8.4 Hz, 1H), 4.44 - 4.08 (m, 2H), 3.77 (s, 3H).

EXAMPLE 16-3 and 16-4



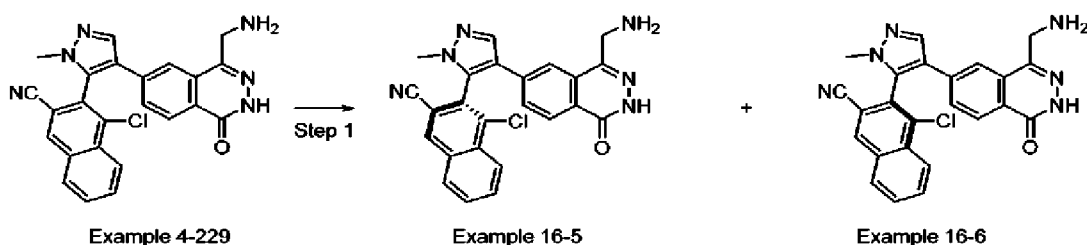
[0586] **Step 1:** To a solution of 2-[4-[4-(aminomethyl)-8-fluoro-1-oxo-2H-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-fluoro-naphthalene-1-carbonitrile (35.0 mg, 0.079 mmol, 1.00 *eq.*) in THF (4 mL) was added Boc_2O (17 mg, 0.079 mmol, 1.00 *eq.*) and the mixture was stirred at rt for 12 hrs. The reaction mixture was then concentrated and the residue purified by prep-TLC (SiO_2 , dichloromethane: methanol 10%) to give *tert*-butyl *N*-[[7-[5-(1-cyano-3-fluoro-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-fluoro-4-oxo-3H-phthalazin-1-yl]methyl]carbamate (30 mg, 0.055 mmol, 70% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 543.2$.

[0587] **Step 2:** To a solution of *tert*-butyl *N*-[[7-[5-(1-cyano-3-fluoro-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-fluoro-4-oxo-3H-phthalazin-1-yl]methyl]carbamate (30 mg, 0.055 mmol, 1.00 *eq.*) in alcohol (2 mL) was added sodium ethoxide (19 mg, 0.276 mmol, 5.00 *eq.*) and the mixture was stirred at 110 °C for 0.75 hr in a sealed tube. The cooled reaction mixture was then filtered, concentrated and the residue triturated with MTBE (1 mL), filtered and dried to give compound *tert*-butyl *N*-[[7-[5-(1-cyano-3-fluoro-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3H-phthalazin-1-yl]methyl]carbamate (30 mg, 0.052 mmol, 96% yield) as a yellow solid. LCMS $[\text{M}+1]^+ = 569.3$.

[0588] **Step 3:** To a solution of *tert*-butyl *N*-[[7-[5-(1-cyano-3-fluoro-2-naphthyl)-1-methyl-pyrazol-4-yl]-5-ethoxy-4-oxo-3H-phthalazin-1-yl]methyl]carbamate (30 mg, 0.052 mmol, 1.00 *eq.*) in dichloromethane (0.2 mL) was added TFA (0.75 mL) and the mixture was stirred at 30 °C for 0.25 hr. The reaction mixture was then concentrated and the residue purified by prep-HPLC (purification method 4-6) then stereoisomers were separated by SFC (DAICEL

CHIRALPAK IG (250 mm × 30 mm, 10 μm); mobile phase: [Heptane-alcohol (0.1% NH₃H₂O)]; B%: 80% isocratic; 7 min cycle, 150 min total) then each stereoisomer was further purified by prep-HPLC (Unisil 3-100 C18 Ultra 150 mm × 50 mm × 3 μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-35%, 10 min) to give example 16-3, 2-[4-[4-(aminomethyl)-8-ethoxy-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-fluoro-naphthalene-1-carbonitrile (1.4 mg, 0.002 mmol, 20% yield,) as a white solid and example 16-4 2-[4-[4-(aminomethyl)-8-ethoxy-1-oxo-2*H*-phthalazin-6-yl]-2-methyl-pyrazol-3-yl]-3-fluoro-naphthalene-1-carbonitrile (1.7 mg, 0.003 mmol, 25% yield,) as a white solid. Spectra data for Example 16-3: LCMS [M+1]⁺ = 569.3; ¹H NMR (400 MHz, MeOD) δ = 8.53 (br s, 2H), 8.33 (d, *J* = 10.0 Hz, 1H), 8.27 (s, 1H), 8.25 - 8.18 (m, 2H), 7.90 - 7.84 (m, 2H), 7.35 (s, 1H), 6.83 (s, 1H), 4.38 - 4.19 (m, 2H), 3.90 (s, 3H), 3.77 - 3.66 (m, 1H), 3.60 - 3.48 (m, 1H), 1.03 (t, *J* = 6.8 Hz, 3H). Spectra data for Example 16-4: LCMS [M+1]⁺ = 569.3; ¹H NMR (400 MHz, CD₃OD) δ = 8.59 - 8.47 (m, 1H), 8.31 (d, *J* = 10.0 Hz, 1H), 8.25 (s, 1H), 8.24 - 8.16 (m, 2H), 7.88 - 7.81 (m, 2H), 7.32 (s, 1H), 6.82 (s, 1H), 4.33 - 4.13 (m, 2H), 3.88 (s, 3H), 3.76 - 3.64 (m, 1H), 3.59 - 3.46 (m, 1H), 1.01 (t, *J* = 6.8 Hz, 3H).

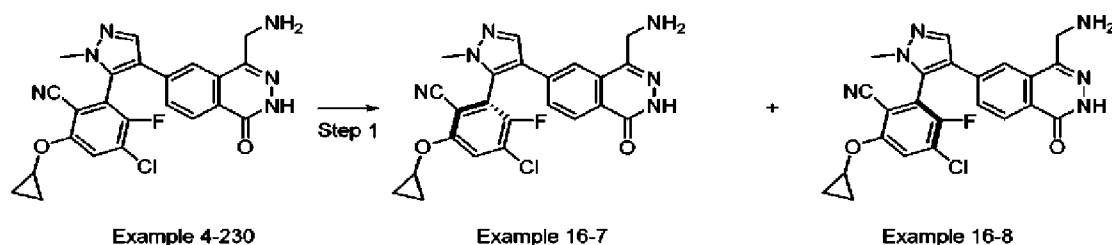
EXAMPLE 16-5 and 16-6



[0589] Example 16-5 (49 mg, 0.112 mmol, 31% yield) and Example 16-6 (48 mg, 0.109 mmol, 30% yield) was separated from Example 4-229 (160 mg, 0.324 mmol) by SFC. MeOH (20 ml) was added to the sample. Waters 80Q instrument, Supercritical CO₂ Flow Rate: 80 g/min Cycle Time: 7 min, total time: 50 min. Single injection volume: 3.0 ml. Back Pressure: 100 bar to keep the CO₂ in Supercritical flow. Phenomenex-Cellulose-2 (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH₃H₂O MeOH]; B%: 60% isocratic). Spectra data for Example 16-5: LCMS [M+1]⁺ = 441.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.82 (s, 1H), 8.94 (s, 1H), 8.48 (s, 1H), 8.44 - 8.39 (m, 1H), 8.32 (br d, *J* = 8.0 Hz, 1H), 8.05 - 7.99 (m, 2H), 7.98 - 7.89 (m, 2H), 7.26 (br d, *J* = 8.4 Hz, 1H), 4.35 (br s, 2H), 3.71 (s, 3H). Spectra data for Example 16-6: LCMS [M+1]⁺ = 441.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.39 (br s, 1H), 8.92 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H),

8.06 - 8.00 (m, 1H), 7.98 - 7.92 (m, 1H), 7.67 (d, $J = 1.6$ Hz, 1H), 7.64 (dd, $J = 1.6, 8.4$ Hz, 1H), 3.73 (s, 3H), 3.54 (s, 2H).

EXAMPLE 16-7 and 16-8



[0590] Example 4-230, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile (30 mg, 0.065 mmol) separated by SFC (DAICEL CHIRALPAK IC (250 mm × 30 mm × 10 μm); mobile phase: [0.1% NH₃H₂O isopropanol]; B%: 40% isocratic, 4.1 min cycle; 120 min total) to give example 16-7 (ee > 99%, 13 mg, 0.026 mmol, 25% yield) as a yellow solid and example 16-8 (8 mg, ee = 84%). Example 16-8 was then then further separated by SFC (DAICEL CHIRALPAK IC (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH₃H₂O EtOH]; B%: 60% isocratic, 3.1 min cycle; total 50 min) to give Example 16-8 (ee > 99%, 4 mg, 0.007 mmol, 7% yield) as a yellow gum. Spectra data for Example 16-7: LCMS [M+1]⁺ = 465.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.59 - 12.44 (s, 1H), 8.29 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 6.0$ Hz, 1H), 7.75 (s, 1H), 7.67 (br d, $J = 7.6$ Hz, 1H), 4.23 - 4.17 (m, 1H), 3.86 (br s, 2H), 3.78 (s, 3H), 0.94 - 0.88 (m, 2H), 0.84 - 0.79 (m, 2H). Spectra data for Example 16-8: LCMS [M+1]⁺ = 465.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.49 - 12.37 (s, 1H), 8.26 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 6.0$ Hz, 1H), 7.73 (d, $J = 1.6$ Hz, 1H), 7.72 - 7.68 (m, 1H), 4.19 (m, 1H), 3.80 (s, 2H), 3.77 (s, 3H), 0.93 - 0.87 (m, 2H), 0.83 - 0.78 (m, 2H).

EXAMPLE A

[0591] This Example illustrates that exemplary compounds of the present invention cooperatively inhibit PRMT5 enzymatic activity in the presence of MTA.

[0592] The PRMT5 inhibitory activity of compounds of the present invention was determined using either a PRMT5:MEP50 FlashPlate Assay (Reaction Biology Corporation) or a PRMT5:MEP50 HotSpot Assay (Reaction Biology Corporation).

1. PRMT5:MEP50 FlashPlate Assay

[0593] The assay uses purified human, PRMT5 enzyme to convert S-adenosyl-L-[methyl-³H]methionine plus histone H4 L-arginine to S-adenosyl-L-homocysteine plus histone H4 [methyl-³H]-L-arginine. The assay was carried out using Streptavidin-coated FlashPlates (Perkin Elmer), which contained a scintillant embedded in the plastic of the plate. The histone H4 peptide substrate was conjugated with biotin, which binds to the streptavidin-coated well of the plate, placing the H4 peptide in close proximity to the side well and the scintillant. The transfer of the tritiated methyl group from S-adenosyl-L-[methyl-³H]methionine to the bound histone H4 peptide generated a radiolabeled histone H4, which was quantitated by measuring in a scintillation counter to determine the activity of PRMT5 enzyme in the presence and absence of compound. The assay reactions also were conducted in the presence and absence of MTA to determine whether the compounds exhibit MTA-cooperative activity. Briefly, compounds of the present invention were solubilized in 100% DMSO at a highest concentration of 10 mM. For IC₅₀ determinations, the initial starting concentration for the serial dilutions of each compound was 50 μM. Control samples lacking compound, PRMT5/MEP50 complex or various reaction components also were prepared and processed in parallel with compound test samples. SAH was used as a positive control for assay validation. To measure PRMT5 inhibitory activity, 3 nM PRMT5/MEP50 complex (Reaction Biology Corporation) was preincubated with test compound in assay buffer containing 40 nM histone H4 peptide (amino acids 1-15)-Biotin conjugate for 20 min at room temperature. The enzymatic reaction was initiated by adding 1 μM tritiated S-adenosyl methionine (final concentration) and the reaction is allowed to proceed for 20 min. The reaction was stopped and the amount of bound, tritiated H4 peptide in each sample was determined using a scintillation counter. The IC₅₀ value for each compound was calculated from each 10-point dose-response curve for samples plus and minus MTA using GraphPad Prism software and the results for exemplary compounds of Formula (I) is shown in Table 9a.

Table 9a

IC₅₀ Values for PRMT5-mediated Enzymatic Activity by Exemplary Compounds of Formula (I) in the Presence and Absence of MTA in the FlashPlate Assay

Example	IC₅₀ + 2 μM MTA (nM)	IC₅₀ (nM)	Example	IC₅₀ + 2 μM MTA (nM)	IC₅₀ (nM)
1-4	39000	>100000	3-48	280	7980
1-5	1400	34800	3-49	110	3850
1-7	1200	31500	3-5	7400	87900
1-8	10000	>100000	3-50	10	277
3-1	3700	89600	3-51	500	11100
3-10	100	3910	3-52	370	3000
3-11	5000	131000	3-53	28	1350
3-12	210000	>1000000	3-54	64	1290
3-13	110	1420	3-55	83	1870
3-14	17	413	3-56	550	11500
3-15	650	18700	3-57	30000	0
3-16	13	186	3-58	510	8070
3-17	770	15100	3-59	7.7	399
3-18	33000	>1000000	3-6	5100	47100
3-19	180	6360	3-60	8100	>100000
3-2	42000	10000	3-61	3.4	80
3-20	53000	0	3-8	>1000000	>1000000
3-21	1800	39400	3-9	33	1230
3-22	35000	>100000	4-1	45000	>100000
3-23	230	6430	4-10	1000	>100000
3-24	20000	>100000	4-100	0.5	80
3-25	71000	>100000	4-101	0.5	17
3-26	1600	20600	4-103	0.5	115
3-27	4200	59000	4-104	0.5	28
3-28	>100000	>100000	4-105	1.8	71
3-29	10000	0	4-106	0.5	56
3-3	25000	10000	4-107	0.5	37
3-30	7700	85200	4-108	900	8650
3-31	80000	>100000	4-109	120	4870
3-32	710	11600	4-11	110	2400
3-33	61	1570	4-110	1000	>100000
3-34	73	2040	4-111	12	472
3-35	59	1530	4-12	7400	>100000
3-36	450	9130	4-13	210	2560

3-37	3200	72100	4-14	7900	>100000
3-38	370	4940	4-15	260	3870
3-39	920	24300	4-16	9.4	602
3-4	1400	38300	4-17	150	2050
3-40	6	193	4-18	280	4420
3-41	1600	27500	4-19	380	>100000
3-42	200	3580	4-2	490	13800
3-43	340	6500	4-61	3	149
3-44	1200	19400	4-62	120	2230
3-45	370	6810	4-63	58	1380
4-20	47	1020	4-64	230	4110
4-21	70	1970	4-65	16	517
4-22	370	8680	4-67	4	204
4-23	>100000	>100000	4-68	10	243
4-24	840	13400	4-69	10	624
4-25	1700	>100000	4-7	8400	>100000
4-26	130	1730	4-70	10	221
4-27	1300	>100000	4-71	4.9	116
4-28	140	6790	4-72	3.0	73
4-29	190	4030	4-73	0.6	24
4-3	37	926	4-74	1.1	76
4-30	400	4750	4-75	0.7	33
4-31	410	7630	4-76	1.3	31
4-32	1.6	45	4-77	1.1	96
4-33	>100000	>100000	4-78	0.5	66
4-34	110	2800	4-79	27	930
4-35	1100	>100000	4-8	440	>100000
4-36	13	541	4-80	58	1570
4-37	1.1	213	4-81	18	826
4-38	25	850	4-82	28	1340
4-39	1.7	109	4-83	14	344
4-4	230	5910	4-84	93	4040
4-40	10	276	4-85	29	1910
4-41	56	4810	4-86	11	731
4-42	45	1380	4-87	22	1590
4-43	32	1520	4-88	45	1710
4-44	5.4	691	4-89	64	1220
4-45	16	291	4-9	590	16000
4-46	0.6	329	4-90	82	2730
4-47	19	667	4-91	16	249
4-48	22.0	750	4-92	3.5	137

4-49	300	5930	4-93	3.3	85
4-5	150	1730	4-94	2.2	83
4-50	22	456	4-95	4.9	228
4-51	5.8	530	4-96	3.9	116
4-52	18	669	4-97	1.6	49
4-53	55	1140	4-98	2.1	90
4-54	77	1550	4-99	15	547
4-55	1.2	30	4-158	2.8	113
4-56	3.8	107	4-159	4.0	68.4
4-57	11	85	5-1	72000	>100000
4-58	1.8	36	5-2	57000	>100000
4-59	2.1	68	6-1	5800	>100000
4-60	2.3	117	7-6	18	577
6-2	>100000	>100000	8-1	47	1650
6-3	9400	>100000	8-2	36	3150
6-4	19000	0	8-3	2.3	237
6-5	>100000	>100000	8-4	3.1	313
7-1	490	11200	8-5	23	691
7-2	16	246	8-6	52	2140
7-3	15	388	8-7	33	931
7-4	5.6	151	8-8	20	795
7-5	2.0	64	9-2	>10,000	N.D.
3-46	570	7880	13-1	25,000	89,600
3-47	56	2950			

[0594] The assay uses recombinant full-length histone H2A as the PRMT5 substrate. Enzymatic transfer of the tritiated methyl group from S-adenosyl-L-[methyl-3H]methionine to the histone H2A protein generated a radiolabeled histone H2A4 by measuring in a scintillation counter to determine the activity of PRMT5 enzyme in the presence and absence of compound. The assay reactions also were conducted in the presence and absence of MTA to determine whether the compounds exhibit MTA-cooperative activity. Briefly, compounds of the present invention were solubilized in 100% DMSO at a highest concentration of 10 mM. For IC₅₀ determinations, the initial starting concentration for the serial dilutions of each compound was 50 μ M. Control samples lacking compound, PRMT5/MEP50 complex or various reaction components also were prepared and processed in parallel with compound test samples. SAH was used as a positive control for assay validation. To measure PRMT5 inhibitory activity, 1 nM PRMT5/MEP50 complex (Reaction Biology Corporation) was

preincubated with test compound in assay buffer containing 5 μ M full-length histone H2A for 20 min at room temperature. The enzymatic reaction was initiated by adding 1 μ M tritiated S-adenosyl methionine (final concentration) and the reaction was allowed to proceed for 60 min. The reaction was stopped and transferred to filter paper for detection. The amount of tritiated H2A in each sample was determined using a scintillation counter. The IC₅₀ value for each compound was calculated from each 10-point dose-response curve for samples plus and minus MTA using GraphPad Prism software and the results for exemplary compounds of Formula (I) is shown in Table 9b.

Table 9b

IC₅₀ Values for PRMT5-mediated Enzymatic Activity by Exemplary Compounds of Formula (I) in the Presence and Absence of MTA in the HotSpot Assay

Example	IC ₅₀ + 2 μ M MTA (nM)	IC ₅₀ (nM)	Example	IC ₅₀ + 2 μ M MTA (nM)	IC ₅₀ (nM)
4-112	1020	-	4-178	4880	-
4-113	561	-	4-179	1240	-
4-114	486	-	4-180	597	-
4-115	377	-	4-181	401	-
4-116	1080	-	4-182	1420	-
4-117	536	-	4-183	2770	-
4-118	724	9924	4-184	127	-
4-119	441	5260	4-185	1160	-
4-120	>10,000	-	4-186	2310	-
4-121	177	-	4-187	239	-
4-122	3820	-	4-188	99	-
4-123	549	-	4-189	656	-
4-124	826	-	4-190	278	-
4-125	1000	-	4-191	612	-
4-126	361	-	4-192	890	-
4-127	2540	-	4-193	>10,000	-
4-128	1310	-	4-194	3820	-
4-129	1650	-	4-195	>10,000	-
4-130	1950	-	4-196	653	-
4-131	1890	-	4-197	719	-
4-132	2560	-	4-198	111	-
4-133	1570	-	4-199	276	-
4-134	2730	-	4-200	156	-
4-107	760	-	4-201	948	-
4-104	794	-	4-202	255	-
3-40	9690	-	4-203	15	-

3-59	1140	>10,000	4-205	23	-
4-32	2040	>10,000	4-206	35	-
4-40	3170	-	4-220	567	-
4-45	2790	-	4-221	501	-
4-36	2800	-	4-222	255	-
4-238	2310	-	4-242	102	-
4-93	845	-	4-106	816	-
4-96	868	>10,000	4-105	1000	-
4-51	1510	>10,000	3-50	3780	>10,000
4-100	1510	>10,000	4-16	8850	-
4-135	641	-	4-71	1050	>10,000
4-136	872	-	4-44	6830	>10,000
4-137	810	-	4-73	933	-
4-138	354	-	4-83	2710	-
4-139	1230	-	4-94	737	-
4-140	1100	-	4-98	635	-
4-141	794	-	4-101	892	-
4-142	881	-	8-9	>10,000	-
4-143	1170	-	9-2	>10,000	-
4-144	454	-	9-3	1273	-
4-145	873	-	9-6	>10,000	-
4-146	569	-	9-7	2559	-
4-147	43	280	10-1	41.7	-
4-148	229	-	10-2	67.2	-
4-149	282	-	10-3	845	-
4-150	673	-	10-4	417	-
4-151	606	-	10-5	1150	-
4-152	978	-	10-6	6630	-
4-152	1910	-	10-7	107	-
4-153	1650	-	10-8	660	-
4-154	3280	-	10-9	1930	-
4-155	3460	-	10-10	2730	-
4-156	9130	-	10-11	34	-
4-158	1460	-	10-12	155	-
4-159	393	-	11-1	1970	-
4-160	1110	-	11-2	138	-
4-161	707	-	12-1	316	-
4-162	842	-	12-2	315	-
4-163	3820	-	12-3	212	-
4-164	464	-	12-4	176	-
4-165	2410	-	12-5	112	-
4-166	4510	-	12-6	730	-
4-167	6620	-	12-7	603	-
4-168	1370	-	12-8	3860	-
4-169	1350	-	12-9	178	-

4-170	728	-	12-11	234	-
4-171	4440	-	12-13	218	-
4-173	1600	-	12-14	182	-
4-174	>10,000	-	14-1	>10,000	-
4-175	1120	-	16-1	38	-
4-176	8710	-	16-2	111	-
4-177	5970	-	16-5	994	-
			16-6	28	-
			16-7	7070	-
			16-8	77	-

EXAMPLE B

Cell-based Assays

[0595] This Example illustrates that exemplary compounds of the present invention are capable of inhibiting proliferation of MTAP-deficient cells.

1. HCT116 MTAP Knockout model

[0596] HCT116 cells were genetically engineered to knock out the function of both MTAP alleles using a CRISPR/Cas9 system and an sgRNA targeting the MTAP gene. Following Cas9/MTAP sgRNA transduction, clones were screened to confirm that each allele of the MTAP gene had been inactivated (i.e., homozygous MTAP knock out) creating an MTAP-deficient cell. Clones confirmed to have a homozygous MTAP knockout were used in cell-based assays to assess the inhibition of PRMT5 and anti-proliferative activity and demonstrate MTA-cooperativity of compounds of the present invention.

2. Proliferation Assays

[0597] Proliferation assays were performed using HCT116 parental and HCT116 homozygous MTAP knockout cell lines to demonstrate increased potency of compounds of the present invention in the MTAP-deficient cells. Control samples were analyzed in parallel.

[0598] Briefly, on Day 0, 250 HCT116 parental or HCT116 homozygous MTAP knockout cell were seeded in 96 well plates in McCoy's 5A supplemented with 10% fetal bovine serum and pen/strep and the cells were incubated overnight at 37°C plus 5% CO₂.

[0599] The following day, cells were treated with DMSO vehicle control or a dose response of PRMT5 inhibitors and incubated at 37C plus 5% CO₂ for five days. On Day 6, the cells

were trypsinized and split 1:10 into new 96-well plates with fresh medium containing the same concentration of PRMT5 inhibitor and incubated for an additional 5 days at 37°C plus 5% CO₂.

[0600] On Day 11, the viability of the cells was measured using a CTG assay kit (CellTiter-Glo; Promega cat.no G7573) in accordance with the manufacturer's instructions. The IC₅₀ values for each compound after 10 days of treatment were calculated using GraphPad PRISM software.

3. SYM11 In-Cell Western

[0601] In-Cell Western assays were performed in HCT116 parental and HCT116 homozygous MTAP Knockout cell lines to demonstrate increased PRMT5 inhibition in the MTAP-deficient cells by measuring the PRMT5-dependent Symmetric Di-methyl Arginine signal. Control samples were analyzed in parallel.

[0602] Briefly, on Day 0, 2,000 HCT116 parental or HCT116 homozygous MTAP knockout cells were seeded in 96 well plates in McCoy's 5A supplemented with 10% fetal bovine serum and pen/strep and the cells were incubated overnight at 37°C plus 5% CO₂. The following day, cells were treated with DMSO vehicle control or a dose response of PRMT5 inhibitors, and incubated at 37°C plus 5% CO₂ for four days.

[0603] After 4 days of treatment, the cells were fixed by adding 50µl of 4% paraformaldehyde solution to each well and the cells were incubated for 20min at room temperature. The paraformaldehyde solution was removed, 150µl of ice-cold methanol was added and the plate was placed -20°C for 10 minutes. The methanol was removed, 150µl of Odyssey Blocking buffer + 0.05% Tween20 was added and the plate was incubated at room temperature with shaking for one hour.

[0604] To each test well, 50µl of SYM11 antibody (Millipore 07-413) diluted 1:500 in Odyssey Blocking buffer + 0.05% Tween20 was added and the plate was placed at 4°C overnight. The primary SYM11 antibody solution was removed by aspiration and the wells were washed three consecutive times with phosphate buffered saline containing 0.1% Tween-20 (PBST).

[0605] A 50µl aliquot of a Goat anti-Rabbit IRDye 800CW secondary antibody (Li-Cor 926-32211) diluted 1:800 and nuclear stain DRAQ5 (Biostatus Limited) diluted 1:10000 in

Odyssey Blocking Buffer + DRAQ5 + 0.05% Tween20 was added and the plate was stored for 2 hours in dark at room temperature. The secondary antibody solution was removed by aspiration and the wells were washed three consecutive times with PBST.

[0606] The SYM11 signal and the DRAQ5 signal were quantified using a Li-Cor Odyssey machine reading at 800nm and 700 nm, respectively. The SYM11/DRAQ5 ratio was used to calculate the inhibition of Symmetric Dimethyl Arginine as percent of DMSO control.

Table 11

Inhibition of PRMT5-dependent Symmetric Di-methyl Arginine (SYM11) signal and proliferation in HCT116 parental and HCT116 homozygous MTAP Knockout cell lines

Example	In-cell-Western (SYM11)		Proliferation	
	HCT116 parental IC ₅₀ (nM)	HCT116 MTAP_KO IC ₅₀ (nM)	HCT116 parental IC ₅₀ (nM)	HCT116 MTAP_KO IC ₅₀ (nM)
4-67	10000	945	7700	2026
4-94	10000	1176	4877	1836
4-100	10000	505	10000	5230
4-101	6667	376	-	2309
4-103	6667	255	-	4391
4-104	3333	391	-	5324
4-105	10000	469	-	1395
4-106	3333	261	-	1596
4-107	10000	31	-	1057
4-127	5920	25	>10,000	615
4-128	4024	39	9633	427
4-129	>10,000	380	>10,000	1347
4-130	>10,000	24	>10,000	756
4-131	3246	43	>10,000	847
4-132	>10,000	24	>10,000	595
4-135	3214	31	6612	3764
4-137	5178	88	>10,000	3236
4-139	5532	254	5067	1488
4-140	>10,000	47	6812	3872
4-141	4958	88	5498	2094
4-142	6273	49	5737	1781
4-145	5487	190	3768	2161
4-146	6693	40	>10,000	261
4-147	1260	11	1906	50

4-148	8552	30	7747	307
4-149	6351	135	>10,000	359
4-150	8392	18	>10,000	661
4-151	5812	51	>10,000	504
4-158	>10,000	>10,000	1742	2200
4-159	>10,000	>10,000	>10,000	8250
4-160	>10,000	944	7700	2026
4-161	6564	87.5	6715	617
4-163	>3333	>3333	>10,000	>10,000
4-164	>10,000	93.3	>10,000	583
4-169	4516	35.5	>10,000	294
4-180	1411	31.9	121	7111
4-181	-	25	-	450
4-182	>1000	58	7252	572
4-183	-	324	-	897
4-184	>10,000	4	9401	107
4-185	-	167	-	3022
4-186	-	5114	-	5775
4-187	1000	7	1363	1903
4-188	>10,000	4	904	39
4-189	1833	31	>10,000	234
4-190	>3333	>3333	-	1977
4-191	-	911	-	1519
4-192	>10,000	256	>10,000	2139-
4-196	1316	11	9289	154
4-197	>1000	25	8572	256
4-198	1266	21	7341	136
4-199	-	2	8846	120
4-200	1752	32	4297	71
4-201	-	16	>10,000	155
4-202	>1000	8	2371	232
4-203	903	2	1210	19
4-204	>1000	12	1830	52
4-205	>1000	6	683	59
4-206	>1000	3	1003	34
4-207	>10,000	3	-	98
4-208	-	11	-	124
4-209	>1000	10	4672	59
4-210	>1000	8	1365	416
4-211	-	197	-	2154

4-212	-	>10,000	-	>10,000
4-213	-	88	-	1679
4-214	-	>10,000	-	4400
4-215	>1000	34	3542	81
4-216	-	83	-	134
4-217	>1000	87	2151	96
4-218	-	140	-	134
4-219	-	>1000	-	3612
4-220		212		5158
4-221	-	196		2379
4-222	-	296	-	5337
4-223	756	12	7808	75
4-224	>1000	10	7808	416
4-225	>1000	17	-5169	84
4-226	-	10	-	191
4-227	-	>1000	-	2367
4-228		>1000		>10,000
4-229	>1000	11	2862	59
4-230	>1000	6	1886	41
4-231	>1000	37	3116	50
4-232	-	148	-	4768
4-233	-	>1000	-	4726
4-234	-	129	-	206
4-235	-	>1000	-	>10,000
4-236	-	>1000	-	>1000
4-237	-	136	-	1044
4-238	-	843	-	1942
4-239	-	>1000	-	>10,000
4-240	-	>1000	-	3563
4-241	>1000	14	2400	51
4-242	>1000	2	4991	44
4-243	-	51	-	285
4-244	-	42	-	327
4-245	-	7	-	8
4-246	-	50	-	72
4-247	-	>1000	-	1806
4-248	-	>1000	-	1161
4-249	-	>1000	-	3508
4-250	-	51	-	757
4-251	-	8	-	49

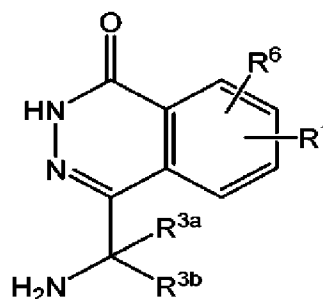
4-252	-	4	-	87
4-254	3333	377	-	2174
9-2	-	>1000	-	>10,000
9-3	-	141	-	4822
9-4	-	>1000	-	4175
9-5	>1000	42	6437	125
9-6	-	>1000	-	>10,000
9-7	-	>1000	-	>10,000
10-1	1123	15	2299	36
10-2	2484	6	3378	112
10-3	3820	5	8482	240
10-4	9215	7	>10,000	128
10-5	>10,000	30	>10,000	250
10-6	>10,000	219	>10,000	4089
10-7	>1000	31	8386	103
10-8	4721	27	>10,000	276
10-9	-	8	9819	489
10-10	>10,000	89	>10,000	1254
10-11	4256	5	763	29
10-12	>1000	6	6196	91
10-13	-	16	-	85
10-14	-	75	-	88
10-15	-	4	-	13
10-16	86	48	1762	86
10-17	-	21	-	21
10-19	-	185	-	312
10-20		29		35
11-1	>1000	57	>10,000	807
11-2	>10,000	1	1952	94
12-1	>1000	28	>10,000	158
12-2	2196	16	208	>10,000
12-3	>1000	8	1686	137
12-4	-	436	-	4366
12-5	-	456	-	3172
12-6	-	380	-	7468
12-7	-	427	-	4985
12-8	-	2856	-	7796
12-9	>10,000	9	3348	148
12-10	>1,000	3	1332	38
12-11	1229	18	8705	125

12-12	-	26	-	240
12-13	>1000	95	1998	1414
12-14	1806	15	>10,000	226
12-15	-	189	-	261
12-16		0.5		75
12-15		189		261
12-16		0.4		73
12-17		10		85
12-18		10		104
13-2	-	64	-	149
13-3	-	298	-	565
15-1	>1000	22	1557	51
15-2	-	96	-	211
16-1	316	2	757	15
16-2	>1,000	73	5925	224
16-3	-	15	-	84
16-4	-	12	-	15
16-5	-	272	-	2850
16-6	-	20	-	64
16-7	-	1000	-	4002
16-8	-	0.8	-	24

[0607] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WE CLAIM:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

R¹ is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C₁ – C₅ alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC₁-C₃alkyl or -Y-heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R²;

each Y is independently a bond or -NR⁴-;

each R² is independently hydroxy, halogen, cyano, cyanomethyl, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C₁ – C₃alkyl, -X-arC₁-C₃alkyl, heteroalkyl, C₂- C₄ alkynyl, -X-haloalkyl, -X-C₁ – C₅ alkyl, -Z-C₁ – C₅ alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵, or;

each X is independently a bond, O, S, -NR⁴- or -NR⁴C(O)-;

each Z is independently a bond, -SO-, -SO₂-, -CH(OH)- or -C(O)-;

each L is independently a bond or C₁ – C₃ alkylene;

R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

each R^4 is independently hydrogen or C1 – C3 alkyl;

each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

2. The compound according to claim 1, wherein R^1 is hydrogen.
3. The compound according to claim 1, wherein R^1 is halogen.
4. The compound according to claim 3, wherein the halogen is bromine.
5. The compound according to claim 1, wherein R^1 is -Y-C1 – C5 alkyl.
6. The compound of claim 5, wherein Y is a bond and the C1 – C5 alkyl is methyl.
7. The compound according to claim 1, wherein R^1 is hydroxyalkyl.
8. The compound according to claim 1, wherein R^1 is -L-CN.
9. The compound according to claim 8, wherein L is C1 – C3 alkylene.
10. The compound according to claim 1, wherein R^1 is -Y-heterocyclyl.
11. The compound according to claim 10, wherein Y is a bond and the heterocyclyl is azetidiny, THFyl or morpholinyl.

12. The compound according to claim 1, wherein R^1 is -Y-aryl, wherein the aryl is optionally substituted with one or more R^2 .
13. The compound according to claim 12, wherein Y is a bond and the aryl is phenyl optionally substituted with one or two R^2 .
14. The compound according to claim 13, wherein the one or two R^2 groups are each independently cyano, halogen or -Y-C1 – C5 alkyl, wherein Y is a bond.
15. The compound according to claim 1, wherein R^1 is -Y-cycloalkyl.
16. The compound according to claim 15, wherein Y is a bond and the cycloalkyl is cyclopentyl.
17. The compound according to claim 1, wherein R^1 is -Y-heteroaryl optionally substituted with one or more R^2 .
18. The compound according to claim 17, wherein Y is a bond and the heteroaryl is pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, triazolyl, oxidazolyl, pyridyl, pyridiazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl, pyrazolopyridinyl, 1*H*-pyrrolopyridyl, pyrazolopyrimidinyl, imidazopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4 λ^4 -imidazopyrimidinyl, 2*H*-4 λ^4 -imidazopyridazinyl, oxazolopyridyl or 5,6-dihydro-8*H*-imidazooxazinyl, each optionally substituted with one or more R^2 .
19. The compound according to claim 18, wherein the heteroaryl is tetrahydropyrazolopyrazinyl, optionally substituted with one or more R^2 .
20. The compound according to claim 19, wherein the tetrahydropyrazolopyrazinyl is substituted with one R^2 selected from the group consisting of -X-C1-C5 alkyl, arC1-C3alkyl, -Z-C1-C5 alkyl, -Z-cycloalkyl and -X-aryl.
21. The compound according to claim 20, wherein R^2 is -Z-cycloalkyl.

22. The compound according to claim 21, wherein Z is a bond and the cycloalkyl is cyclopropyl.
23. The compound according to claim 21, wherein Z is -C(O)- and the cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclo[1.1.1]pentyl.
24. The compound according to claim 17, wherein the heteroaryl is pyridyl, optionally substituted with one or two R².
25. The compound according to claim 24, wherein the pyridyl is substituted with one R².
26. The compound according to claim 25, wherein R² is hydroxy, halogen, cyano, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C1 - C3alkyl, arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 - C5 alkyl, -Z-C1 - C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵.
27. The compound according to claim 26, wherein R² is -X-C1 - C5 alkyl, and X is a bond and the C1 - C5 alkyl is methyl, ethyl, propyl, or isopropyl.
28. The compound according to claim 26, wherein R² is -X-haloalkyl, and X is a bond and the haloalkyl is difluoromethyl or trifluoromethyl.
29. The compound according to claim 26, wherein R² is -X-haloalkyl, X is O and the haloalkyl is difluoromethyl or trifluoromethyl.
30. The compound according to claim 26, wherein R² is -X-L-cycloalkyl, wherein X is a bond, L is a bond and the cycloalkyl is cyclopropyl.
31. The compound according to claim 26, wherein R² is -X-L-cycloalkyl, wherein X is a bond, L is a methylene and the cycloalkyl is cyclopropyl or cyclohexyl.
32. The compound according to claim 26, wherein R² is -X-L-cycloalkyl, wherein X is O, L is methylene and the cycloalkyl is cyclopropyl.

33. The compound according to claim 26, wherein R^2 is C2- C4 alkynyl, wherein the C2- C4 alkynyl is ethynyl or prop-2-ynyl.
34. The compound according to claim 26, wherein R^2 is $-SO_2C1 - C3$ alkyl, wherein the C1 - C3 alkyl is methyl.
35. The compound according to claim 26, wherein R^2 is heterocyclyl, wherein the heterocyclyl is morpholinyl or tetrahydropyranlyl.
36. The compound according to claim 26, wherein R^2 is -X-heteroaryl, wherein the heteroaryl is optionally substituted with one or more R^5 .
37. The compound according to claim 36, wherein X is a bond, and the heteroaryl is pyrazolyl substituted with one R^5 , wherein R^5 is C1 - C3 alkyl.
38. The compound according to claim 36, wherein the X is a bond, and the heteroaryl is pyridyl or pyrimidinyl, each optionally substituted with one or more R^5 .
39. The compound according to claim 36, wherein the X is a bond or O, and the heteroaryl is quinolinyl optionally substituted with one or more R^5 .
40. The compound according to claim 36, wherein the X is $-NR^4-$, and the heteroaryl is quinolinyl optionally substituted with one or more R^5 .
41. The compound according to claim 36, wherein R^2 is -X-aryl, wherein the aryl is optionally substituted with one or more R^5 .
42. The compound according to claim 41, wherein X is a bond and the aryl is phenyl or naphthyl substituted with one, two or three R^5 .
43. The compound according to claim 42, wherein each R^5 is selected from the group consisting of cyano, halogen, -X-L-cycloalkyl, -X-haloalkyl, heterocyclyl, X-heteroaryl, C1 - C3 alkyl and alkoxy.

44. The compound according to claim 41, wherein X is O and the aryl is phenyl substituted with one or two R⁵.
45. The compound according to claim 44, wherein each R⁵ is cyano, halogen, C1 – C3 alkyl or alkoxy.
46. The compound according to claim 41, wherein X is S, the aryl is phenyl substituted with one R⁵, wherein R⁵ is halogen or C1 – C3 alkyl.
47. The compound according to claim 41, wherein the X is -NR⁴-, and the aryl is phenyl optionally substituted with one or more R⁵.
48. The compound according to claim 26, wherein R² is halogen, wherein the halogen is chlorine or fluorine.
49. The compound according to claim 18, wherein the heteroaryl is pyrazolopyridinyl, optionally substituted with one or more R².
50. The compound of claim 49, wherein the pyrazolylpyridinyl is substituted with one R², wherein the one R² is alkoxy or -X-aryl.
51. The compound of claim 45, wherein the alkoxy is methoxy or isopropoxy.
52. The compound of claim 45, wherein the -X-aryl, the X is O and the aryl is phenyl.
53. The compound according to claim 1, wherein R¹ is -Y-aryl, wherein Y is -NR⁴- and the aryl is phenyl optionally substituted with one or more R⁵.
54. The compound according to claim 1, wherein R¹ is -Y-C1- C5 alkyl, wherein Y is -NR⁴- and the C1 – C5 alkyl is methyl, ethyl or propyl.
55. The compound according to claim 1, wherein R¹ is -Y-arC1-C3alkyl, wherein Y is -NR⁴- and the arC1-C3alkyl is benzyl.
56. The compound according to claim 24, wherein the pyridyl is substituted with two R².

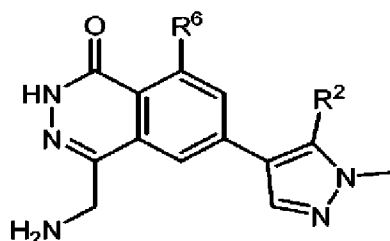
57. The compound according to claim 56, wherein each R^2 is -X-C1 – C5 alkyl or one R^2 is halogen or -X-L-cycloalkyl and the second R^2 is -X-C1 – C5 alkyl, wherein each X is a bond.
58. The compound according to claim 18, wherein the heteroaryl is pyrimidinyl, optionally substituted with one or more R^2 .
59. The compound according to claim 58, wherein the pyrimidinyl is substituted with one R^2 .
60. The compound according to claim 59, wherein R^2 is -X-C1 – C5 alkyl or -X-haloalkyl.
61. The compound according to claim 18, wherein the heteroaryl is pyrazolyl, optionally substituted with one, two or three R^2 groups.
62. The compound according to claim 61, wherein the pyrazolyl is substituted with one R^2 .
63. The compound according to claim 62, wherein R^2 is -X-C1 – C5 alkyl, hydroxyalkyl, arC1-C3alkyl, or -X-aryl optionally substituted with one or more R^5 .
64. The compound according to claim 63, wherein R^2 is -X-C1 – C5 alkyl, wherein the X is a bond, and the C1 – C5 alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl.
65. The compound according to claim 61, wherein the pyrazolyl is substituted with two independently selected R^2 .
66. The compound according to claim 65, wherein the two R^2 groups are (1) independently -X-C1 – C5 alkyl, (2) -X-C1 – C5 alkyl and halogen, (3) -X-C1 – C5 alkyl and alkoxy, (4) -X-C1 – C5 alkyl and -N(R^4)₂, (5) X-C1 – C5 alkyl and -X-haloalkyl, (6) -X-C1 – C5 alkyl and arC1-C3alkyl, (7) -X-C1 – C5 alkyl and -X-L-cycloalkyl, (8) -X-C1 – C5 alkyl and -heterocyclyl, (9) -X-C1 – C5 alkyl and -X-aryl

optionally substituted with one or more R⁵, (10) -X-C1 – C5 alkyl and -X-heteroaryl optionally substituted with one or more R⁵, (11) -X-C1 – C5 alkyl and cyanomethyl, (12) -X-C1 – C5 alkyl and cyano, (13) cyano and halogen, wherein the halogen is chlorine or fluorine, (14) cyano and -X-L-cycloalkyl, (15) independently halogen, (16) cyano and alkoxy, wherein each X is a bond, (17) cyano and -X-aryl, (18) cyano and -X-heteroaryl, (19) cyano and heterocyclyl (20) halogen and -X-arC1-C3alkyl or X-arC1-C3alkyl substituted with cyano, and (21) halogen and -X-aryl.

67. The compound according to claim 66, wherein the pyrazolyl is substituted with -X-C1 – C5 alkyl and -X-aryl optionally substituted with one or more R⁵, wherein the X is a bond and the aryl is phenyl substituted with two R⁵, wherein each R⁵ is independently -X-C1 – C5 alkyl, wherein each X is a bond; one R⁵ is cyano and one R⁵ is -X-C1 – C5 alkyl, wherein each X is a bond; one R⁵ is cyano and one R⁵ is -X-L-cycloalkyl, wherein X is a bond and L is a bond, methylene or ethylene; one R⁵ is cyano and one R⁵ is halogen; one R⁵ is cyano and one R⁵ is alkoxy; or each R⁵ is independently halogen.
68. The compound according to claim 66, wherein the pyrazolyl is substituted with -X-C1 – C5 alkyl and -X-aryl optionally substituted with one or more R⁵, wherein the X is a bond and the aryl is phenyl substituted with three R⁵, wherein each R⁵ is -X-C1 – C5 alkyl, wherein each X is a bond; one R⁵ is cyano and two R⁵ are -X-C1 – C5 alkyl, wherein each X is a bond; one R⁵ is cyano, one R⁵ is halogen, and one R⁵ is -X-C1 – C5 alkyl, wherein X is a bond; one R⁵ is cyano and two R⁵ are alkoxy, one R⁵ is cyano and two R⁵ are halogens, one R² is cyano and two R² are halogen; one R² is cyano, one R² is halogen and one R² is alkoxy, or one R² is alkoxy, and two R² are independently halogen.
69. The compound according to claim 18, wherein the heteroaryl is imidazolyl, 1*H*-pyrrolopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4λ⁴-imidazopyrimidinyl, 2*H*-4λ⁴-imidazopyridazinyl, or oxazolopyridyl, each substituted with one R² group, wherein each R² is -X-C1 – C5 alkyl, wherein X is a bond.

70. The compound according to claim 18, wherein the heteroaryl is imidazopyridyl substituted with one R^2 group, wherein R^2 is cyano, alkoxy, halogen or -X-C1 – C5 alkyl and X is a bond.
71. The compound according to claim 18, wherein the heteroaryl is imidazopyridyl substituted with two R^2 groups, wherein one R^2 group is halogen and the second R^2 group is -X-C1 – C5 alkyl, wherein X is a bond, or halogen.
72. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} are each hydrogen.
73. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} are each deuterium.
74. The compound according to any of claims 2-71, wherein one of R^{3a} and R^{3b} is hydrogen and the other is deuterium.
75. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} together are oxo.
76. The compound according to any of claims 2-75, wherein R^4 is hydrogen.
77. The compound according to any of claims 2-75, wherein R^4 is methyl.
78. The compound according to any of claims 2-77, wherein R^6 is hydrogen.
79. The compound according to any of claims 2-77, wherein R^6 is halogen.
80. The compound of claim 79, wherein the halogen is chlorine or fluorine.
81. The compound according to any of claims 2-77, wherein R^6 is C1 – C3 alkyl.
82. The compound according to claim 81, wherein the C1 – C3 alkyl is methyl or ethyl.
83. The compound according to any of claims 2-77, wherein R^6 is alkoxy.

84. The compound according to claim 83, wherein the alkoxy is methoxy.
85. The compound according to any of claims 2-77, wherein R^6 is haloalkyl.
86. The compound according to claim 85, wherein the haloalkyl is trifluoromethyl.
87. A compound of Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

each Y is independently a bond or $-NR^4$ -;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2C1 - C3alkyl$, $-X-arC1-C3alkyl$, heteroalkyl, $C2- C4$ alkynyl, $-X-haloalkyl$, $-X-C1 - C5 alkyl$, $-Z-C1 - C5 alkyl$, heterocyclyl, $-X-L-$ cycloalkyl, $-Z-cycloalkyl$, $-X-aryl$, $-Z-aryl$, or $-X-heteroaryl$, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5 , or;

each X is independently a bond, O, S, $-NR^4$ - or $-NR^4C(O)-$;

each Z is independently a bond, $-SO-$, $-SO_2-$, $-CH(OH)-$ or $-C(O)-$;

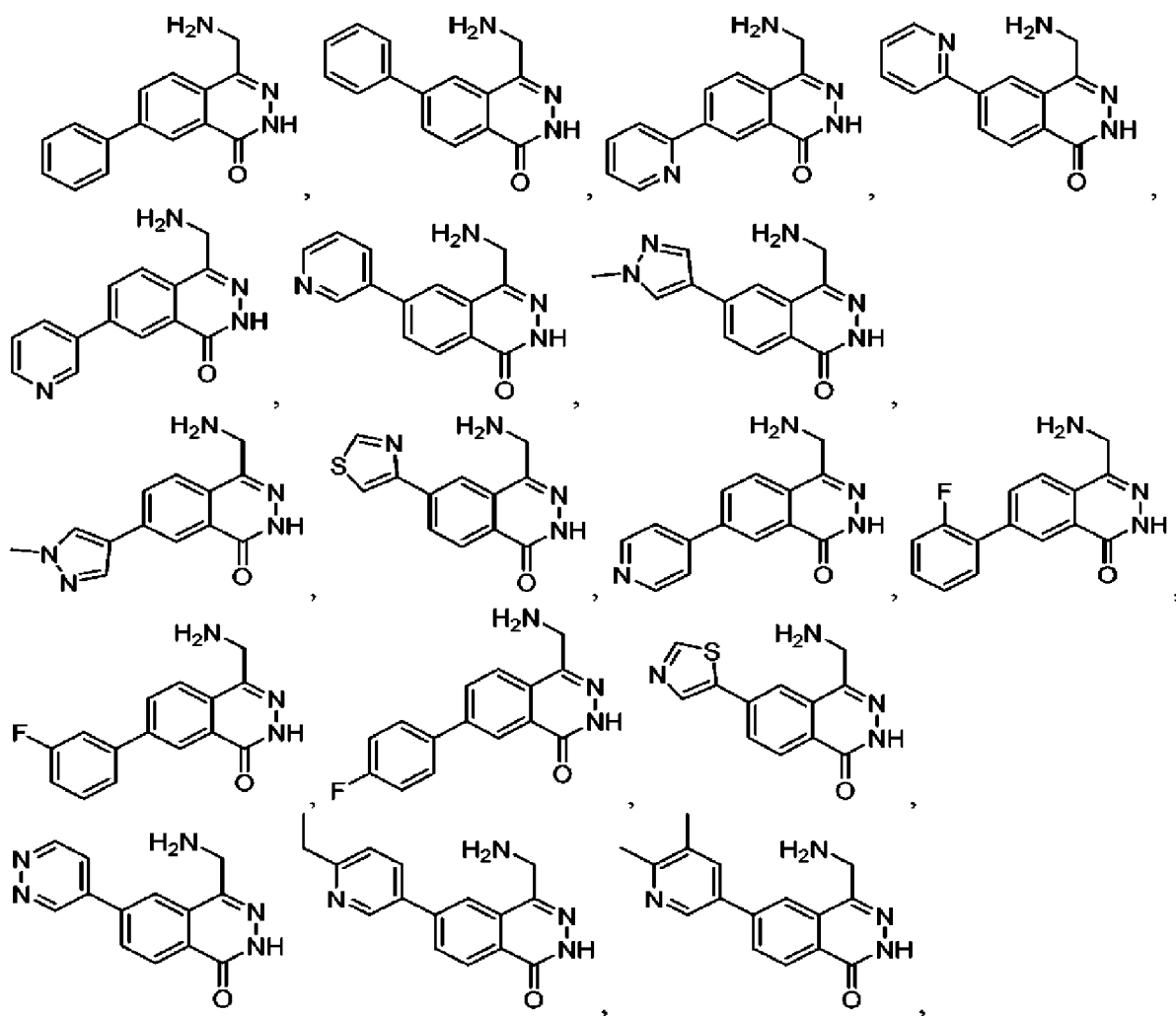
each L is independently a bond or $C1 - C3$ alkylene;

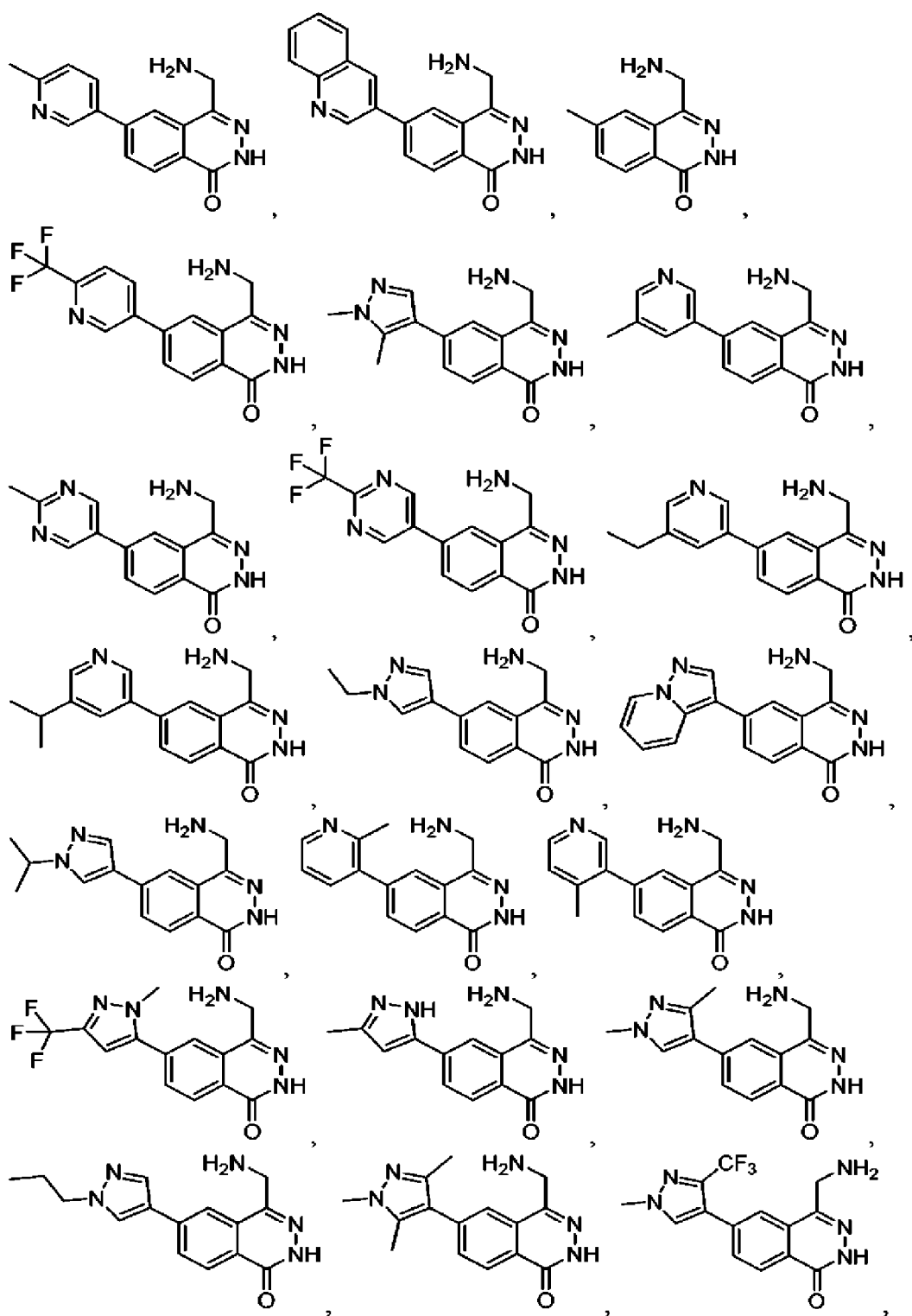
each R^4 is independently hydrogen or $C1 - C3$ alkyl;

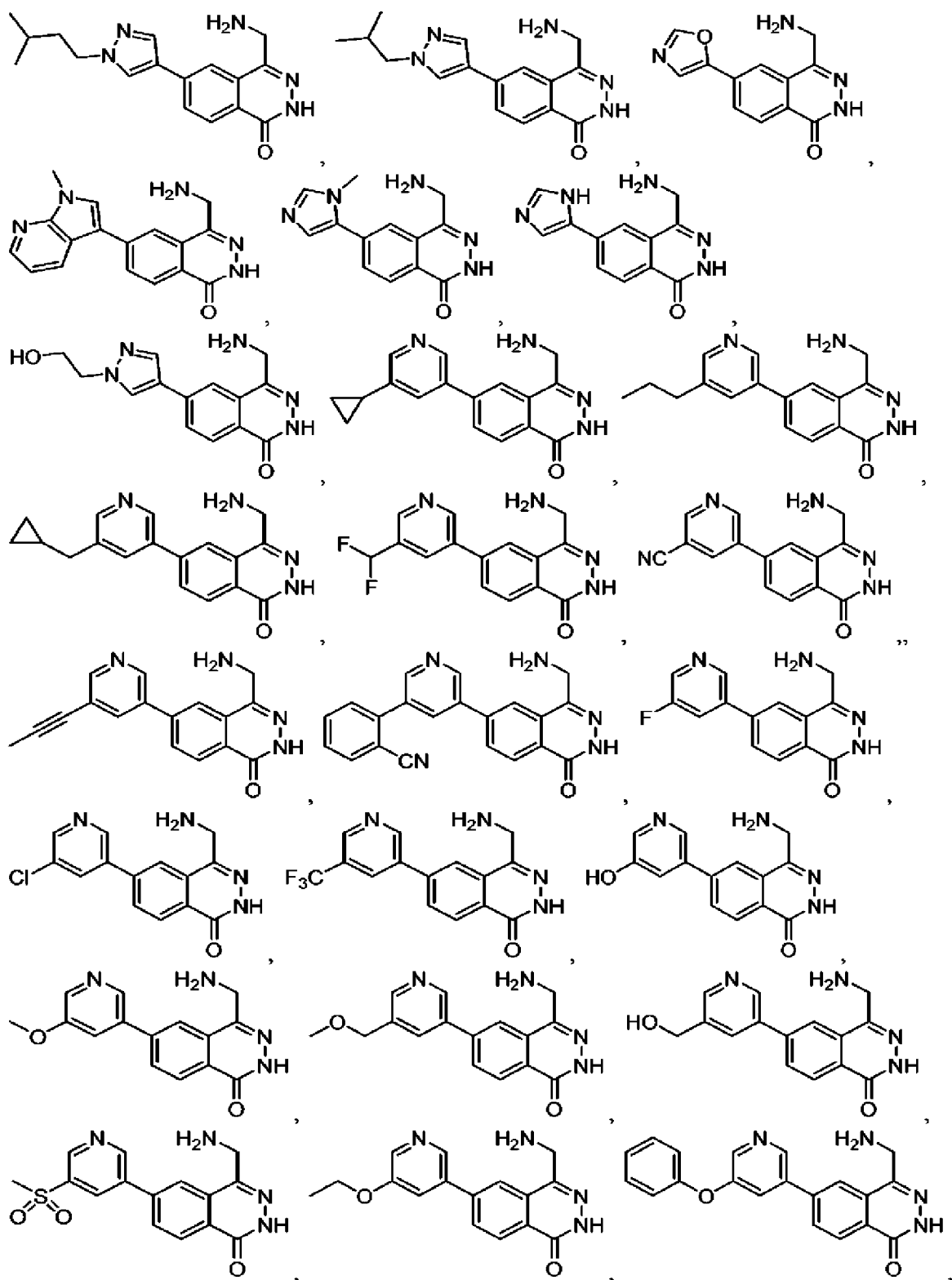
each R⁵ is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

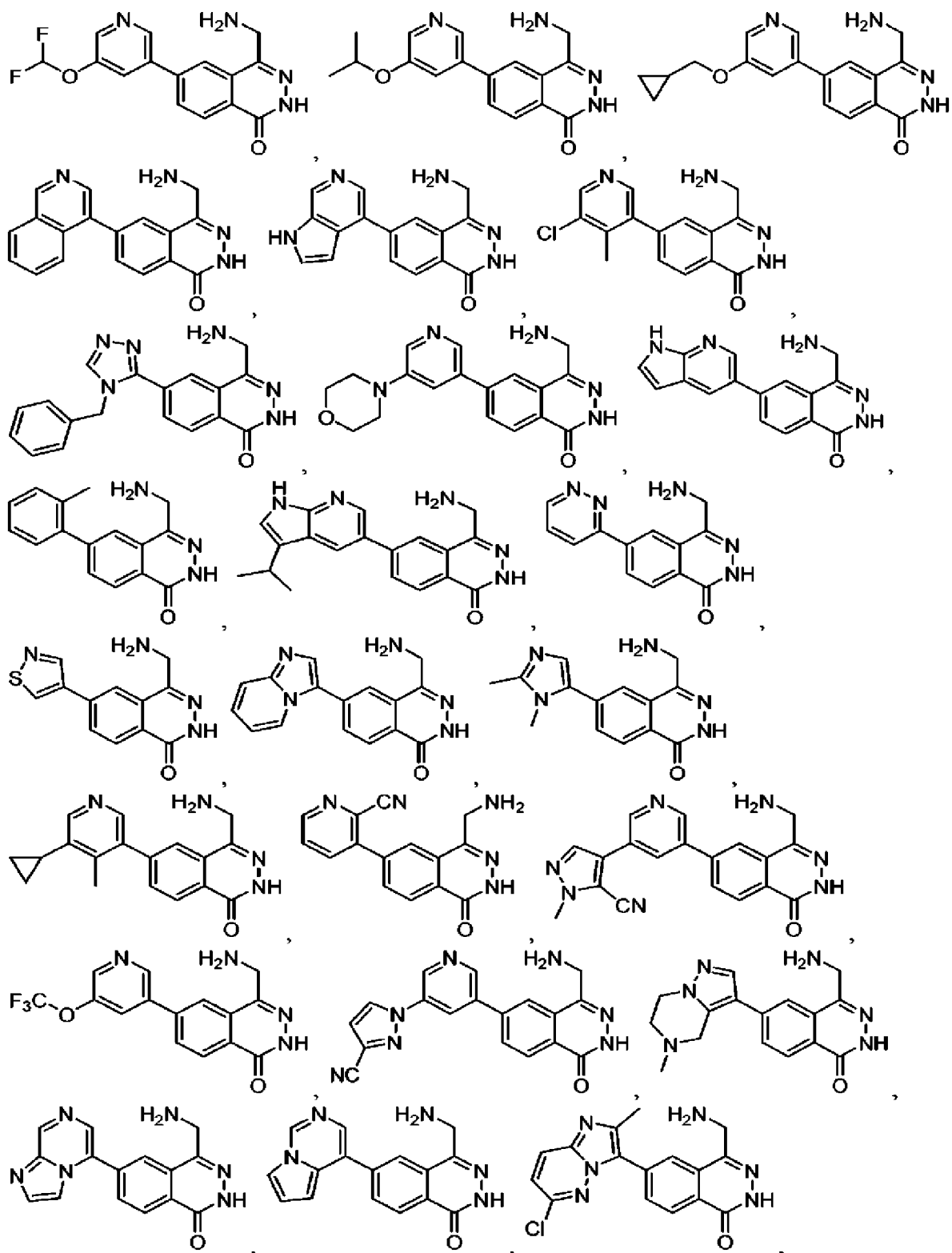
R⁶ is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

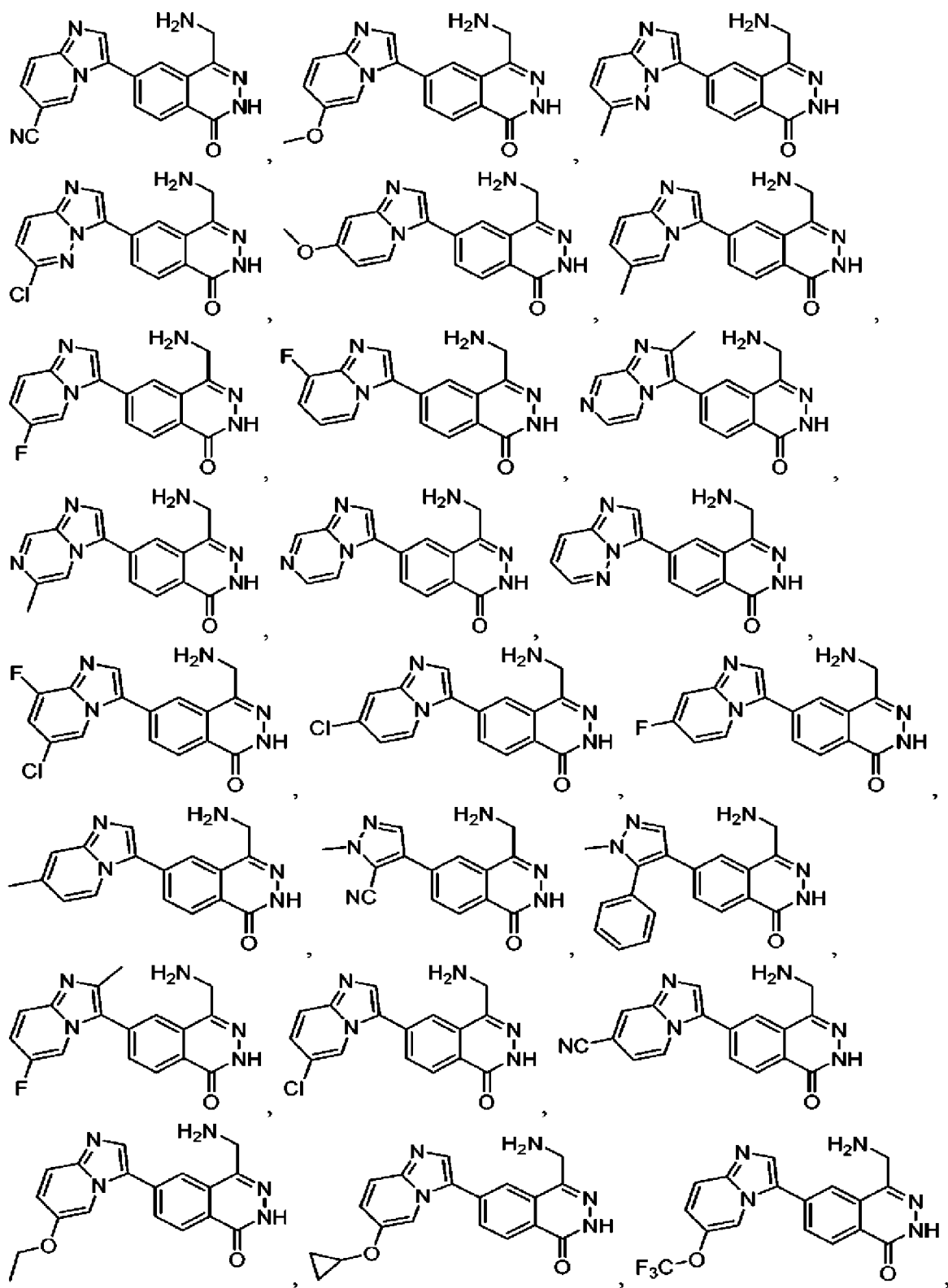
88. The compound of claim 1, wherein the compound is:

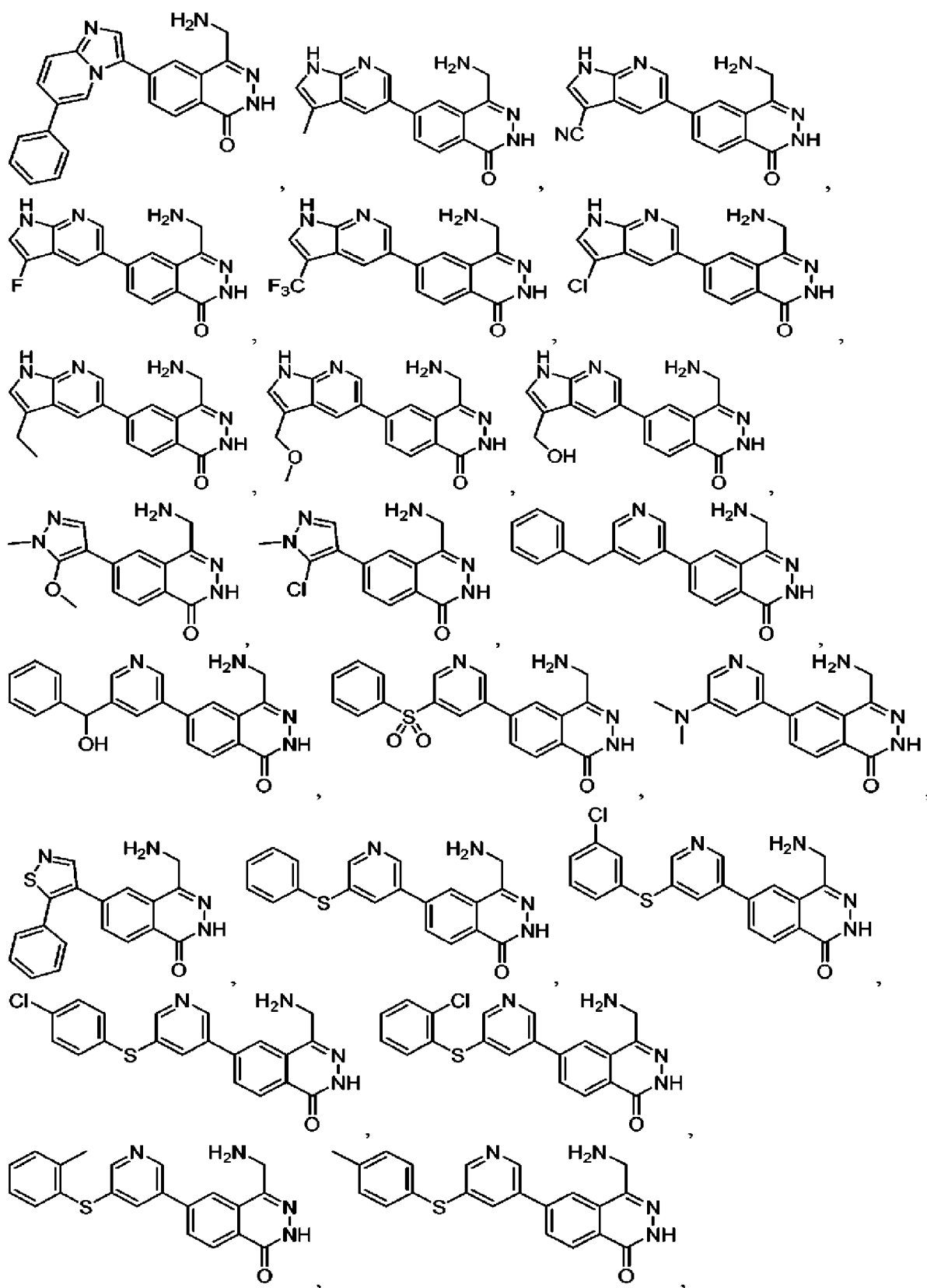


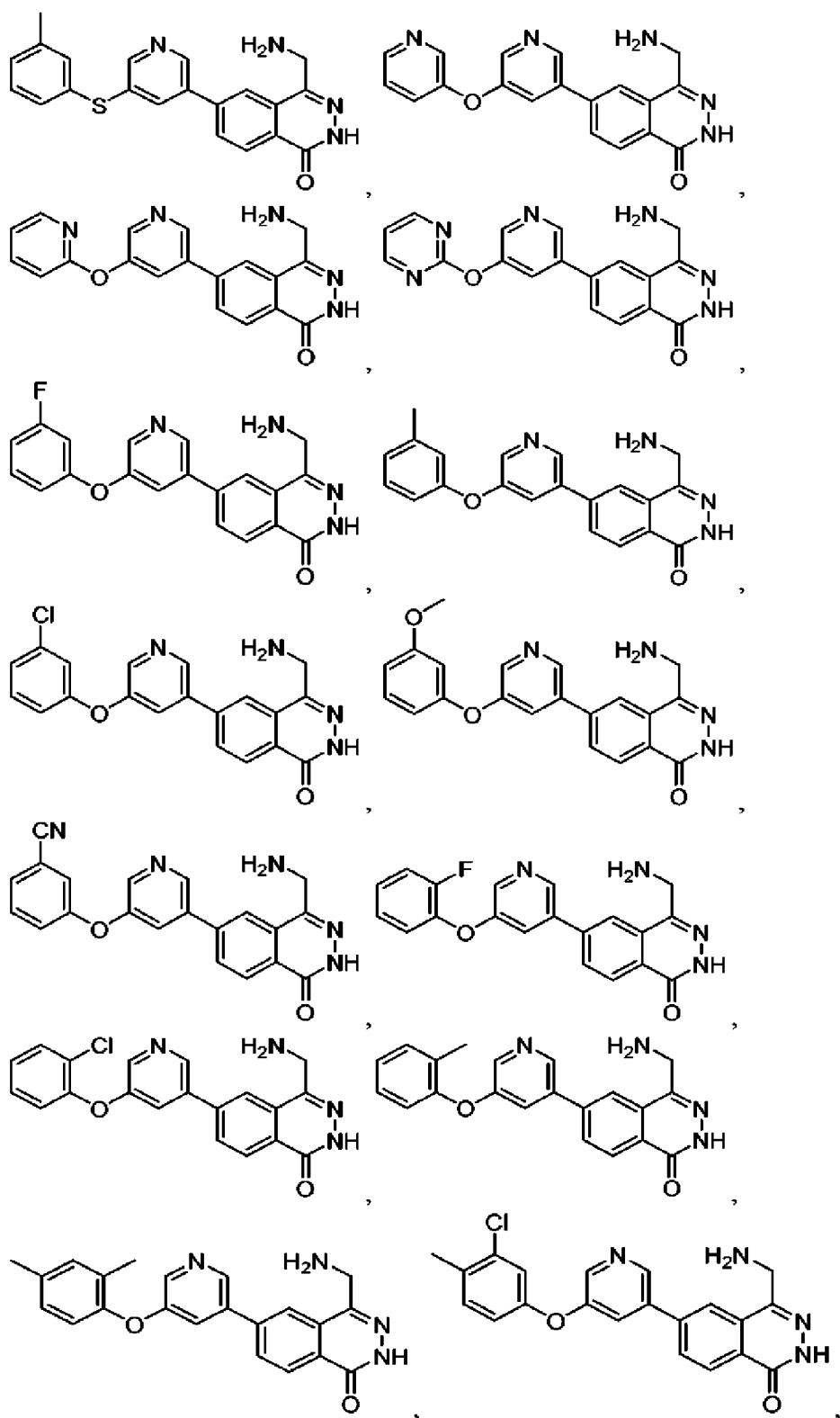


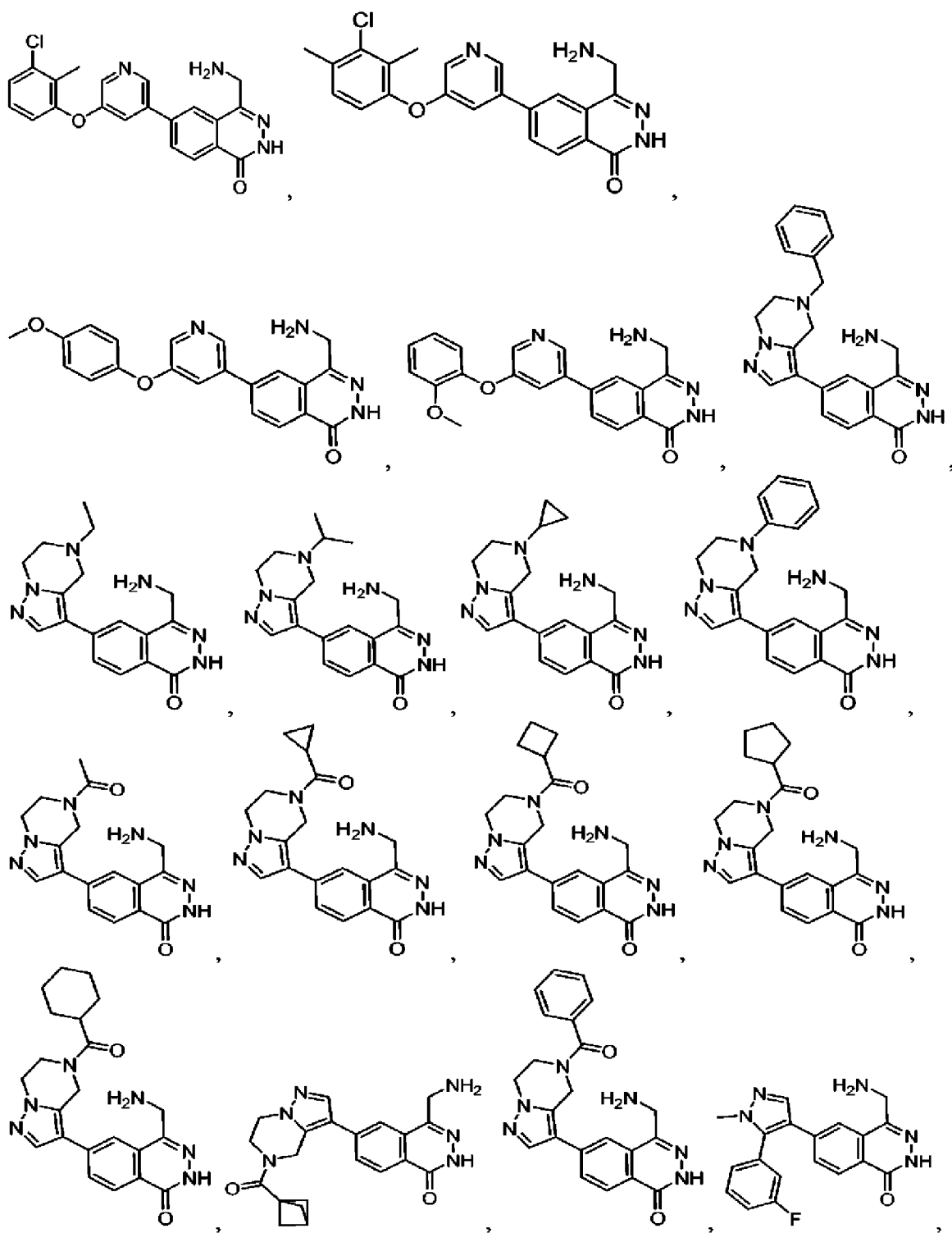


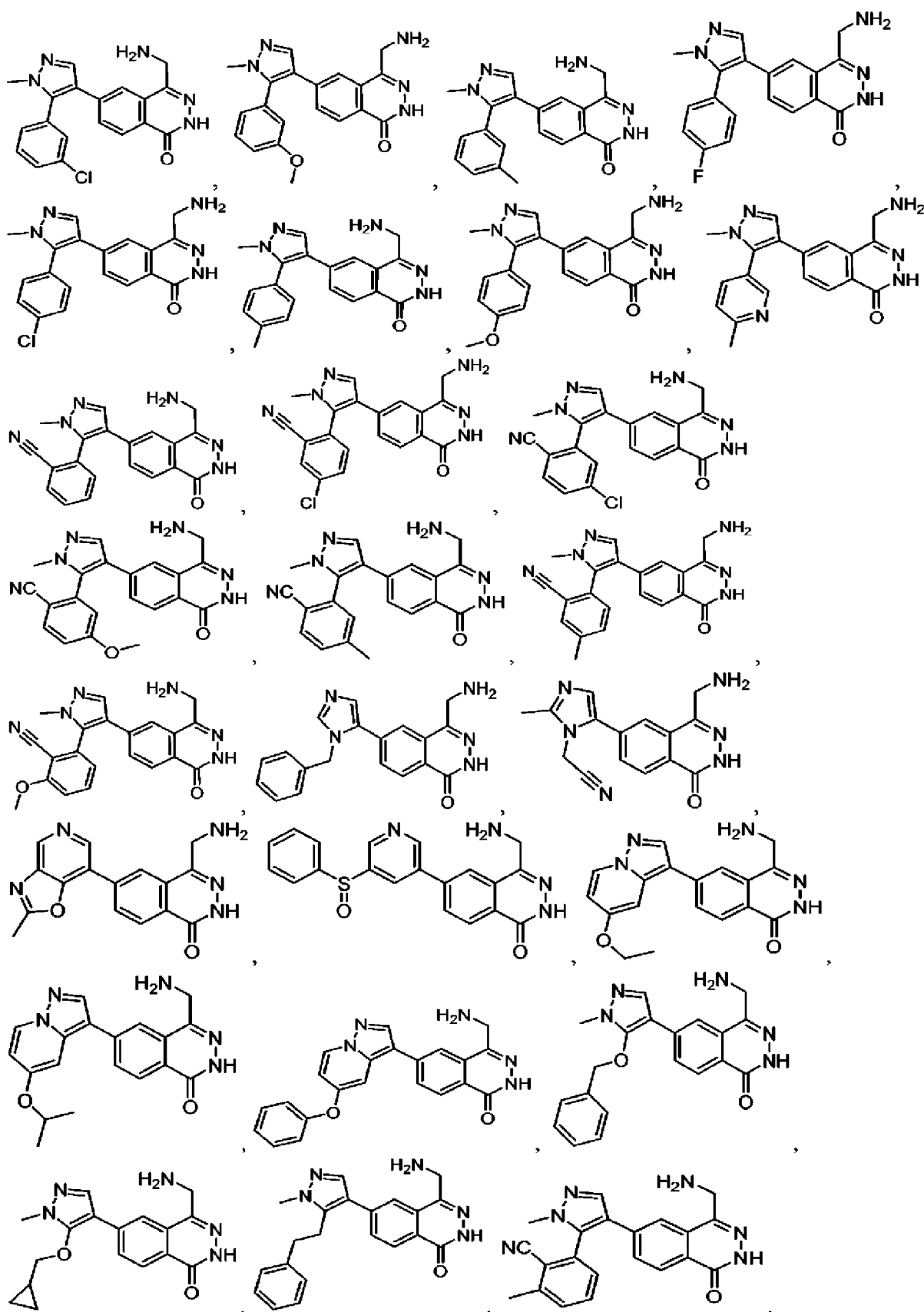


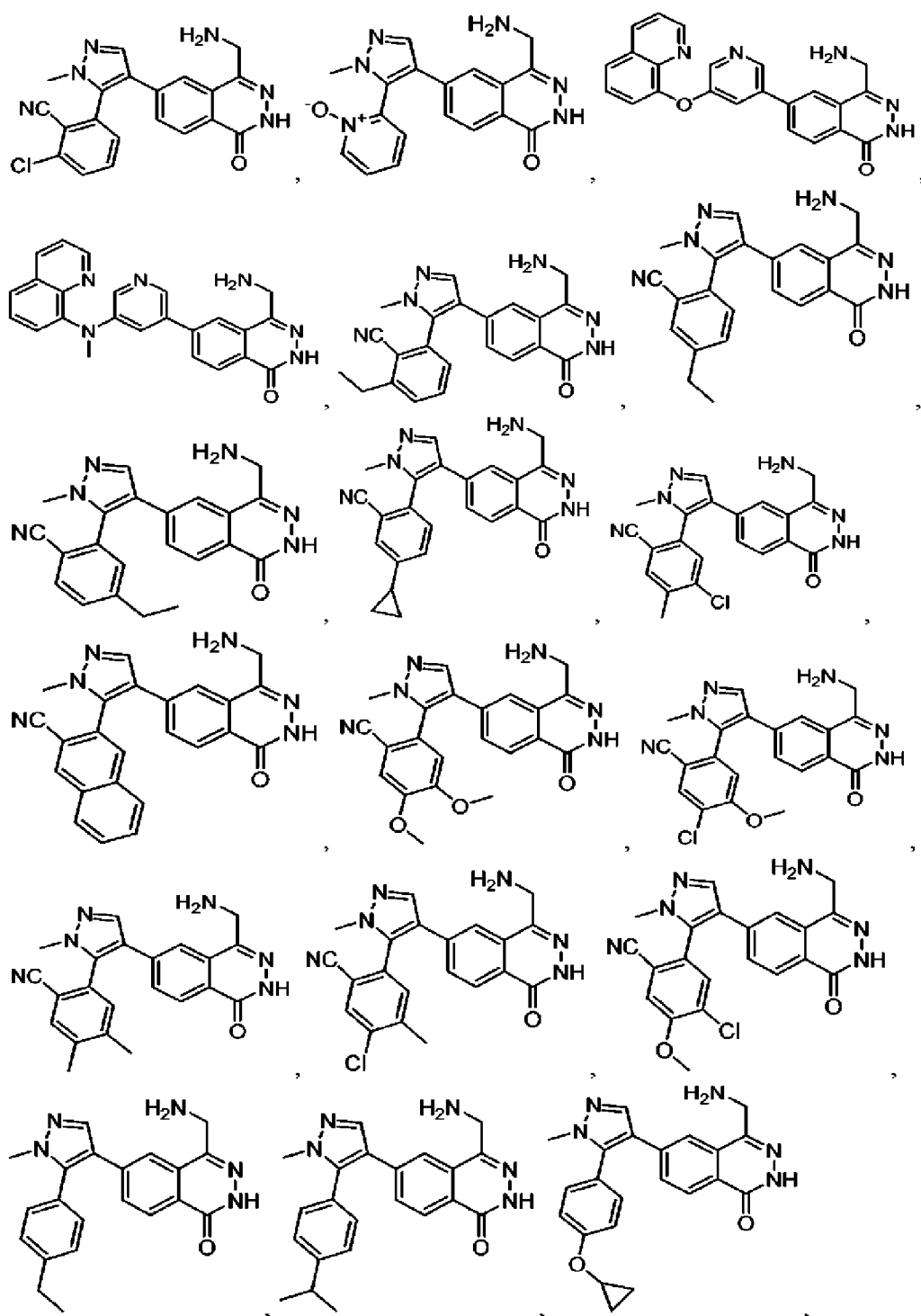


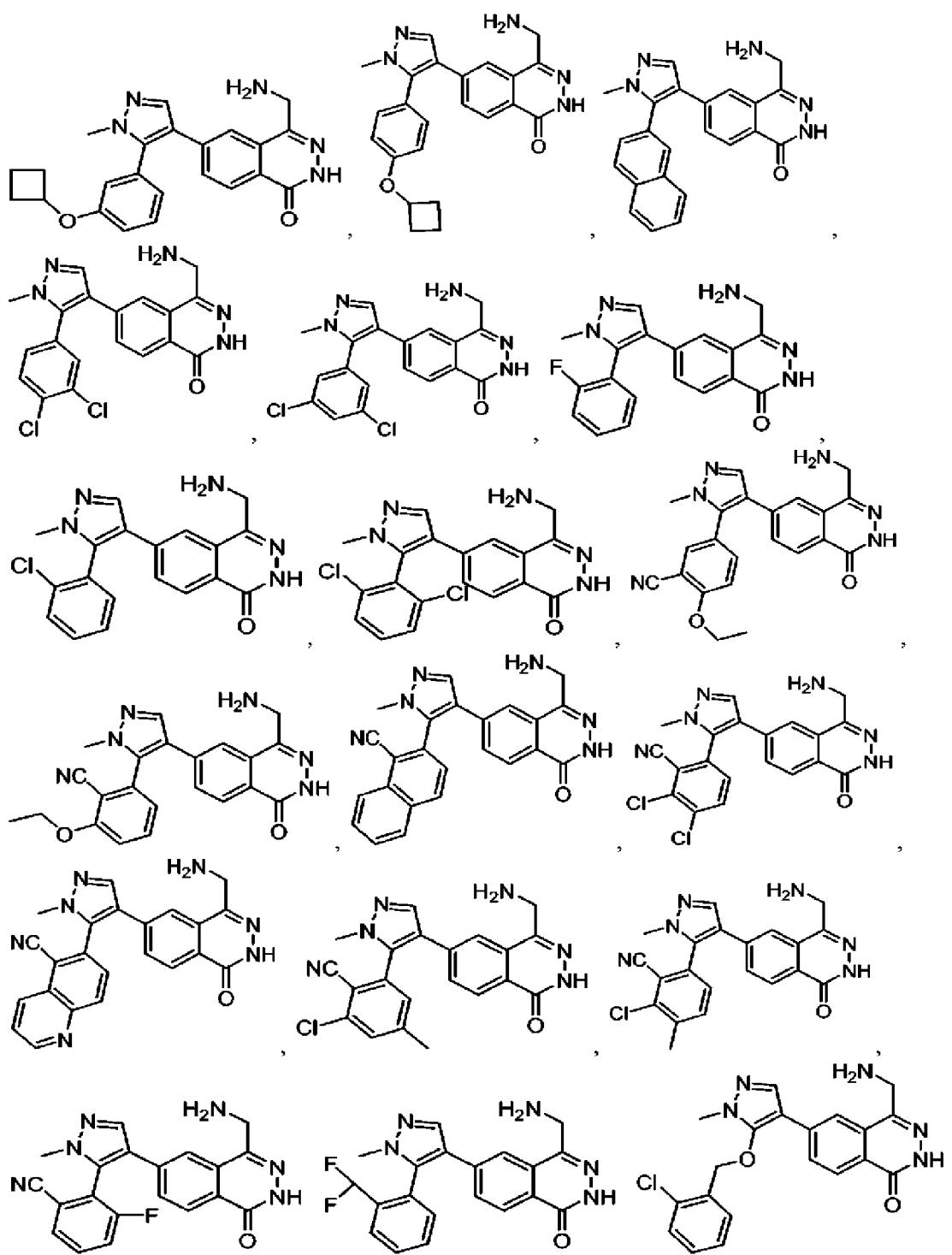


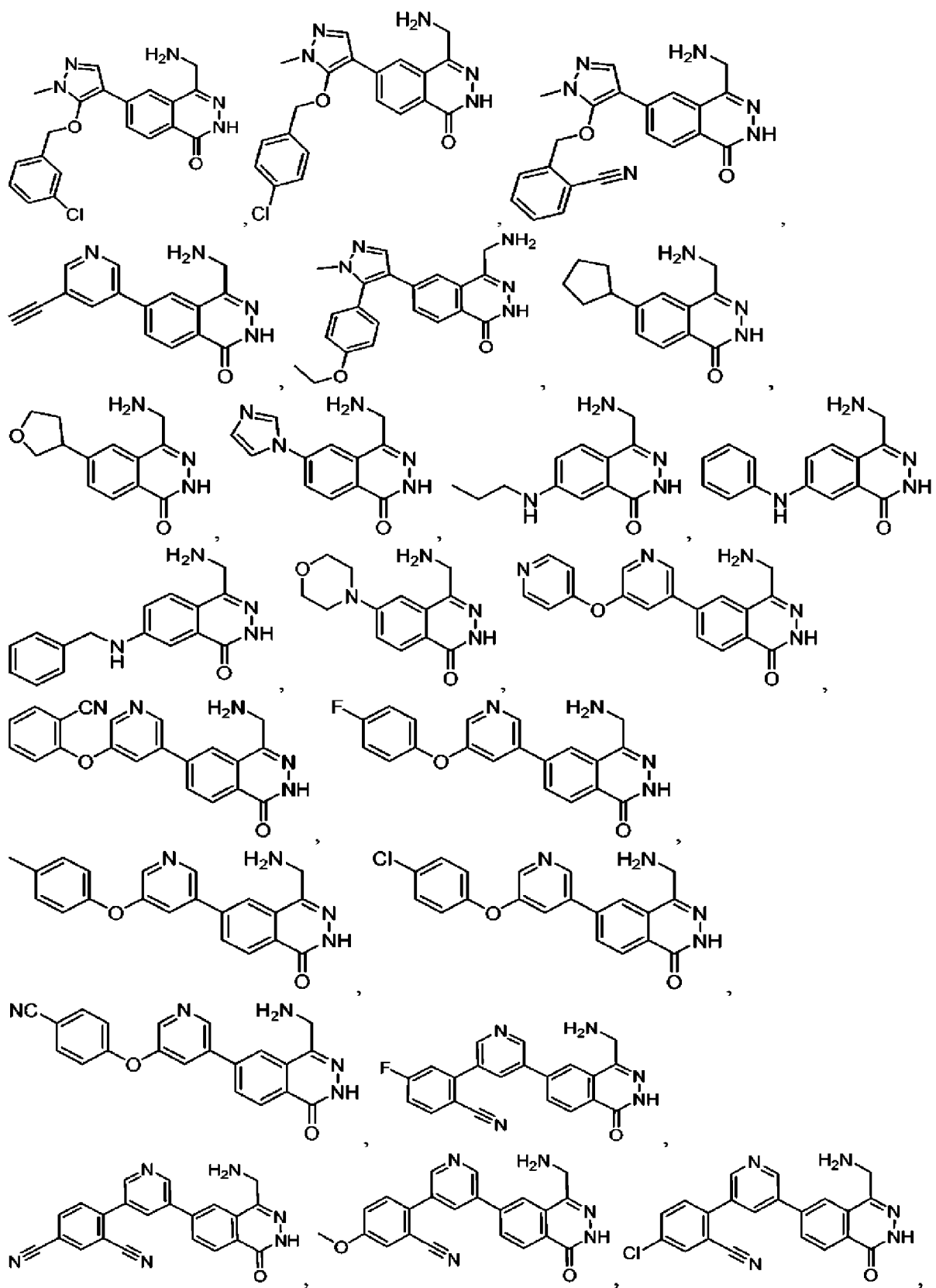


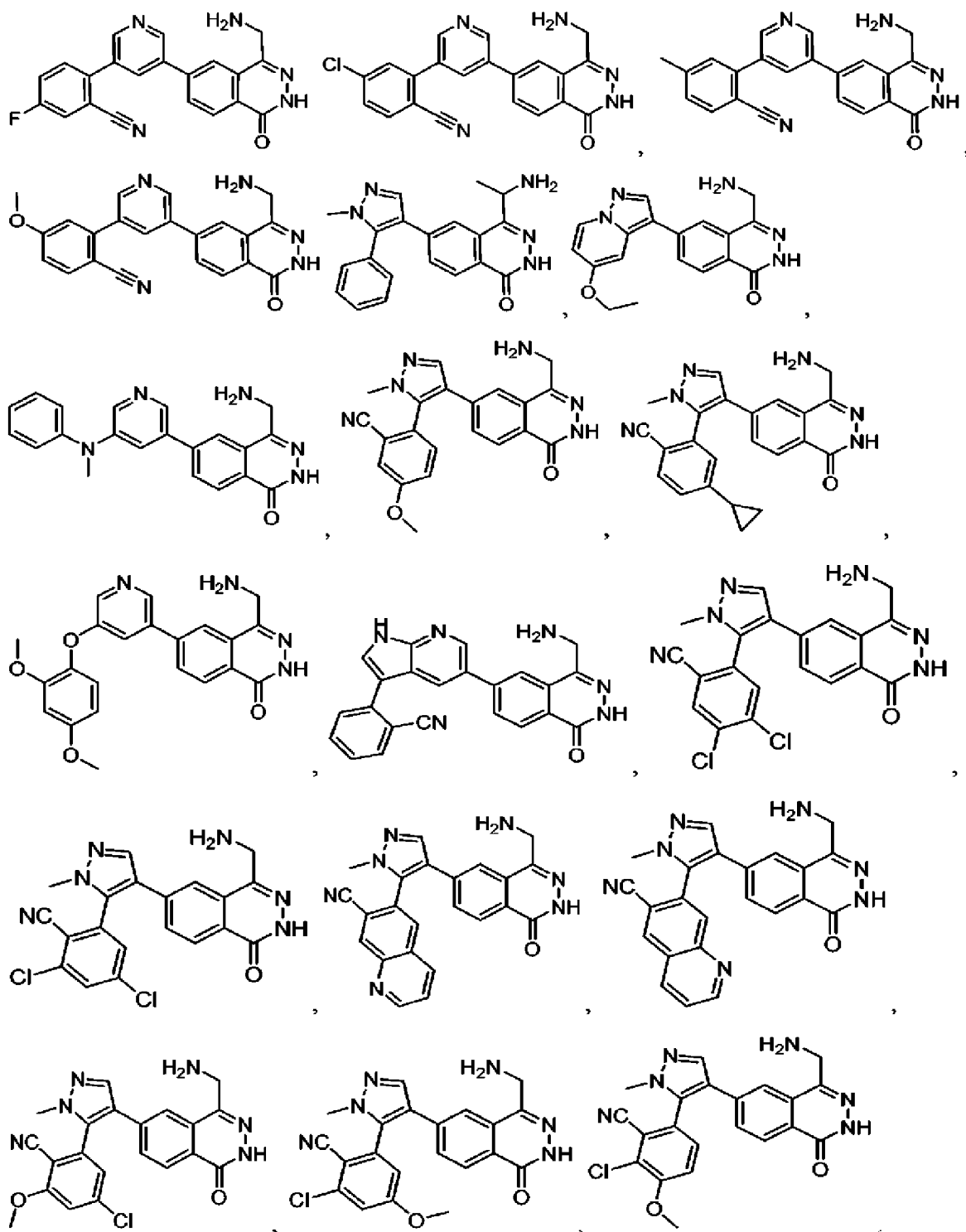


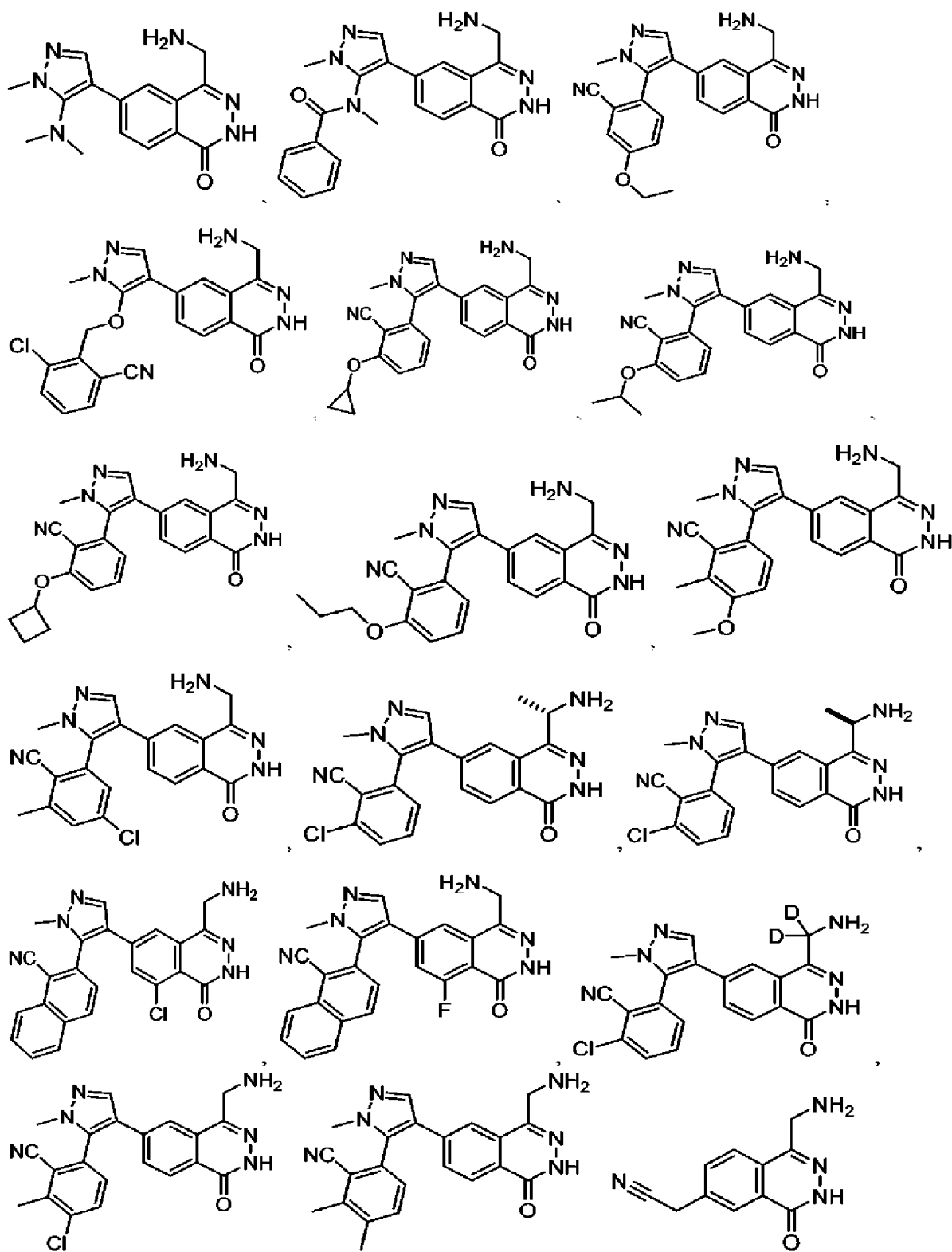


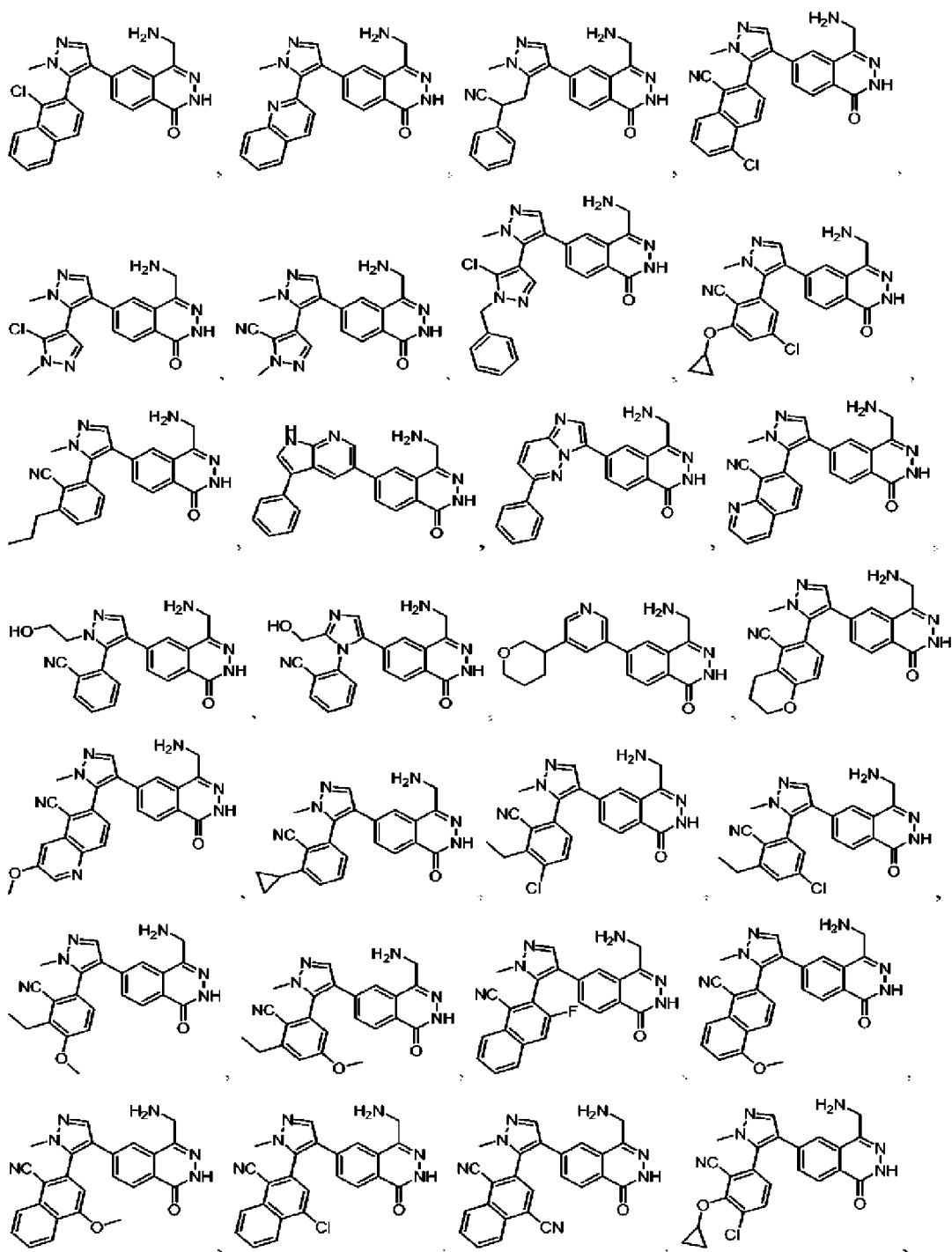


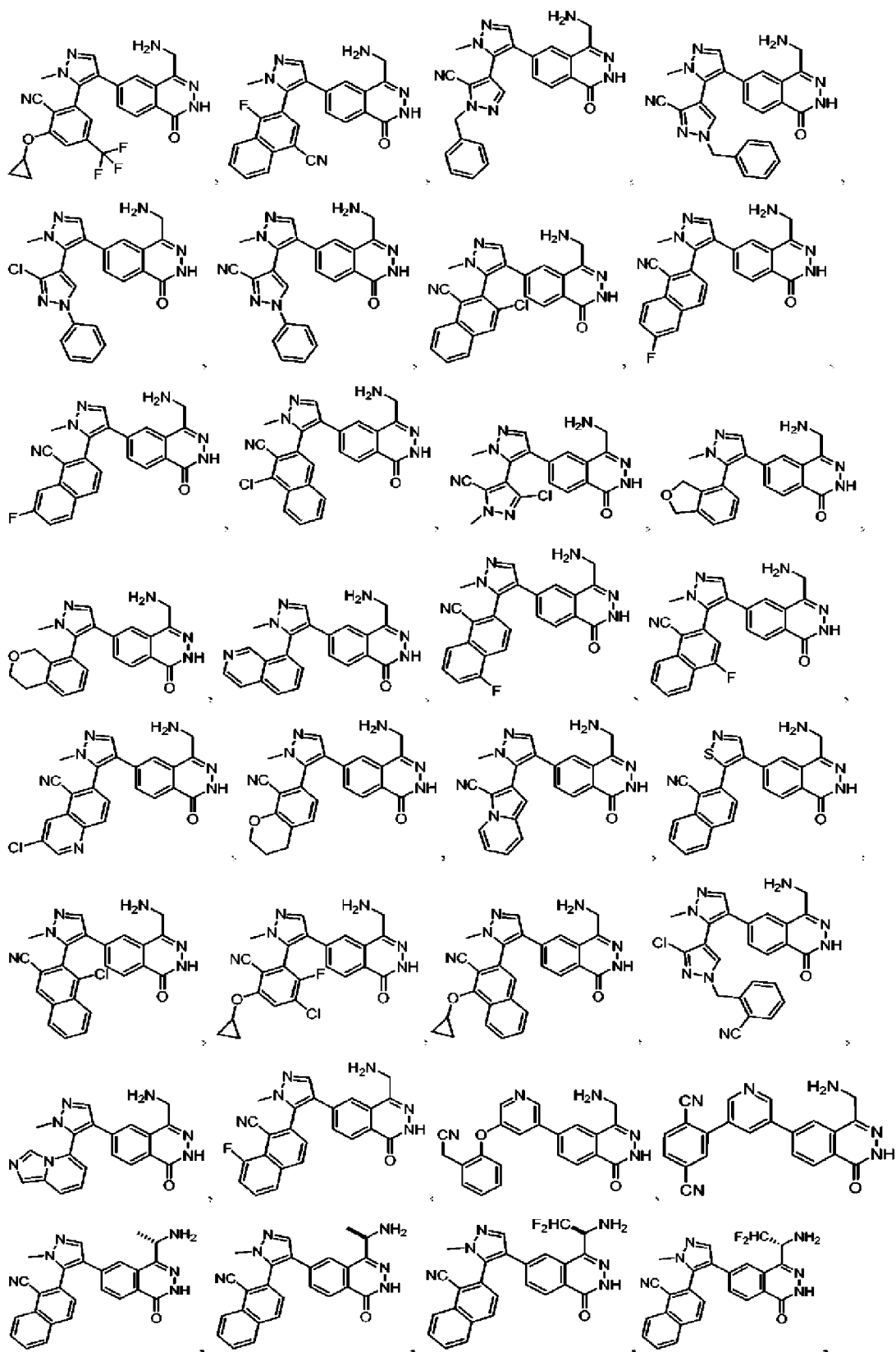


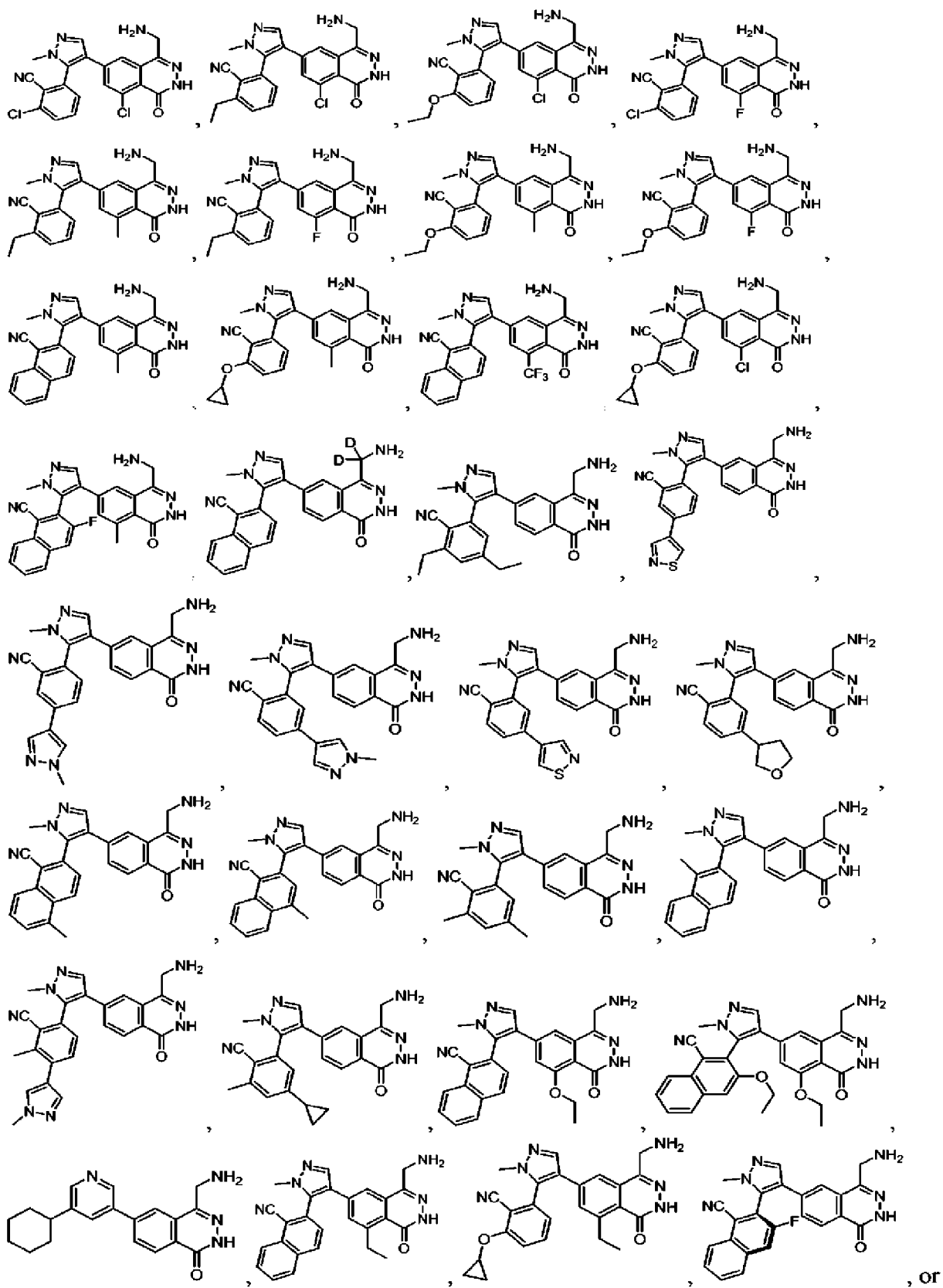


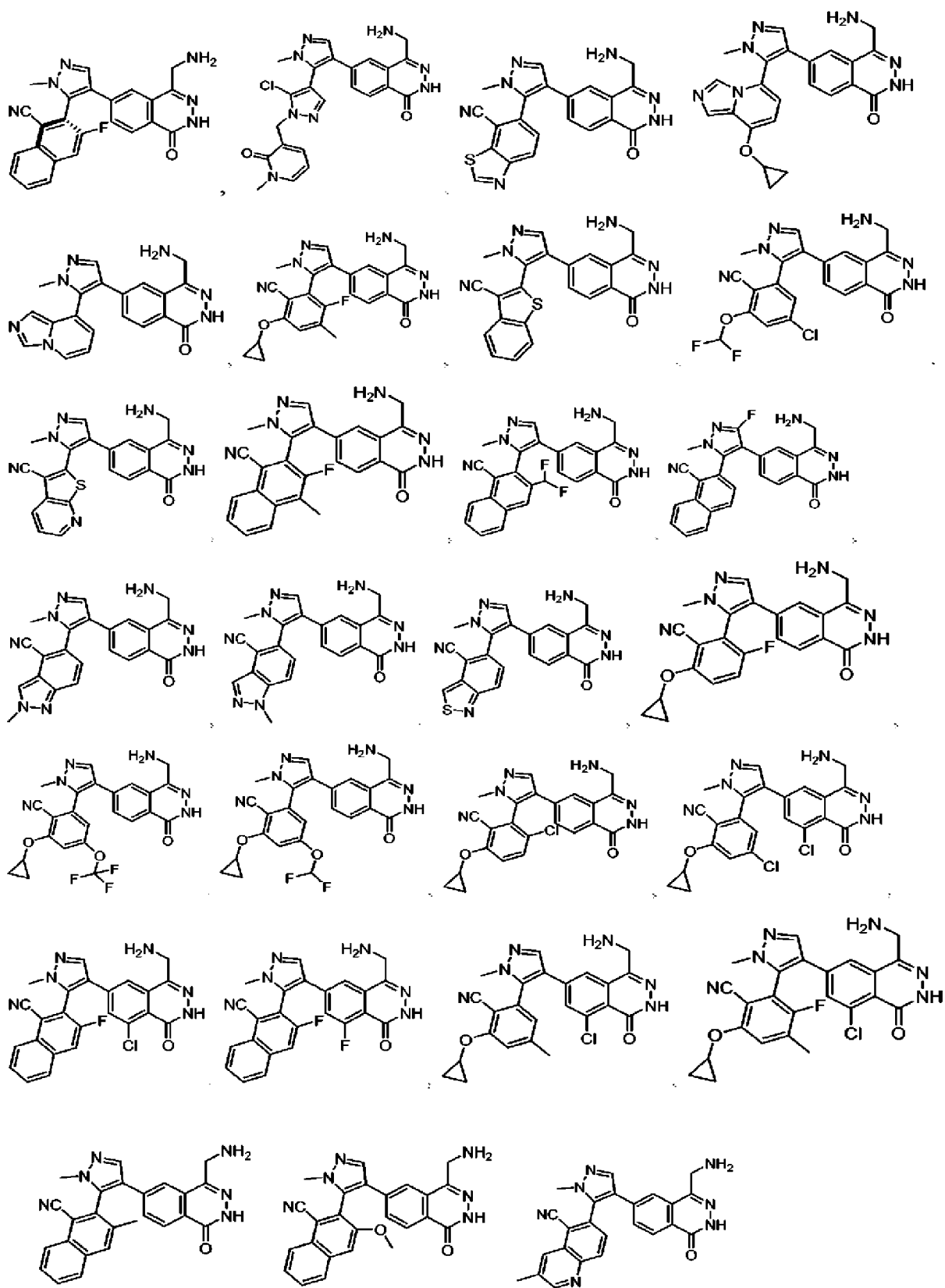


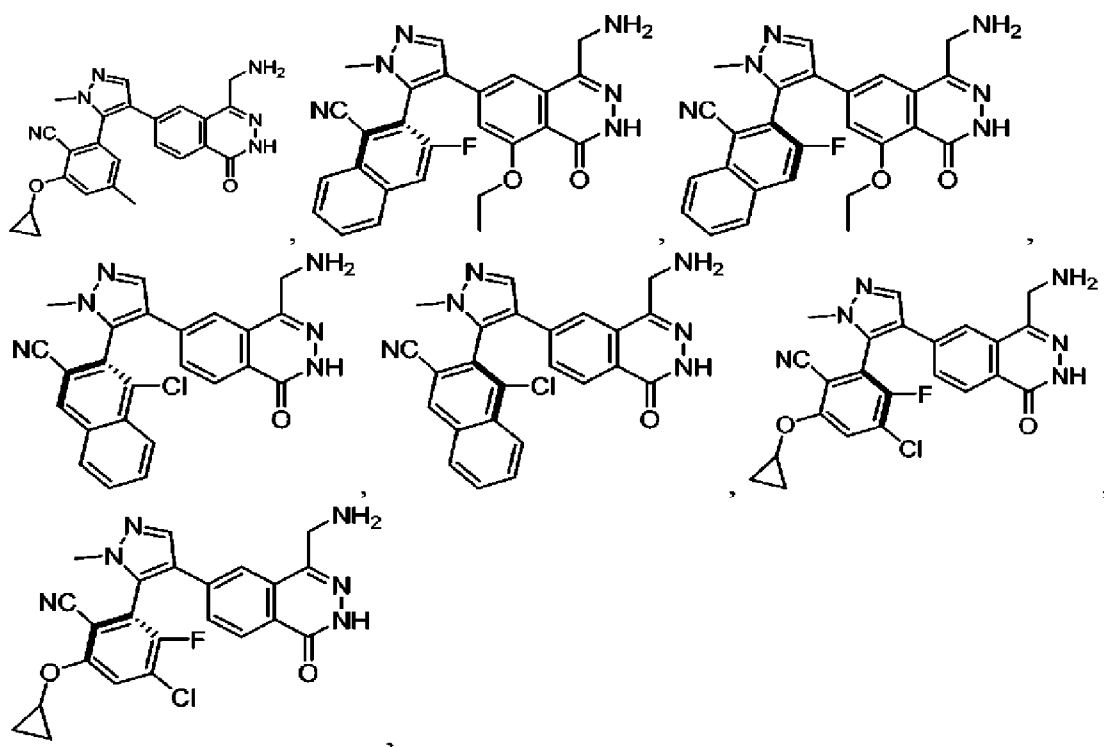






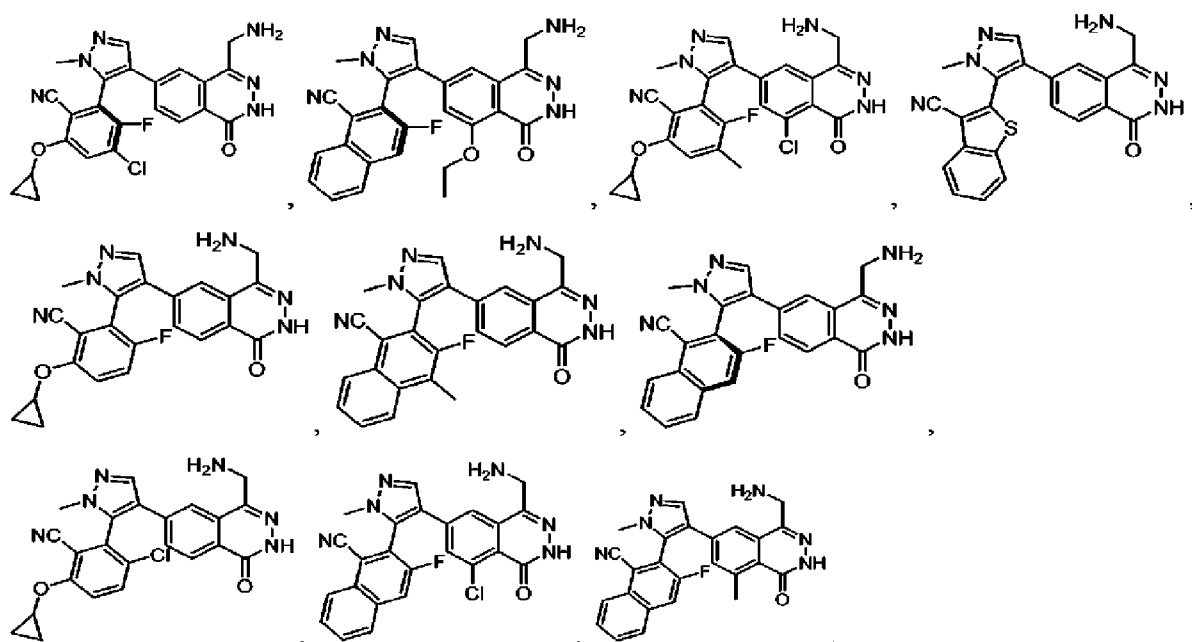






or a pharmaceutically acceptable salt thereof.

89. The compound of claim 1, wherein the compound is:



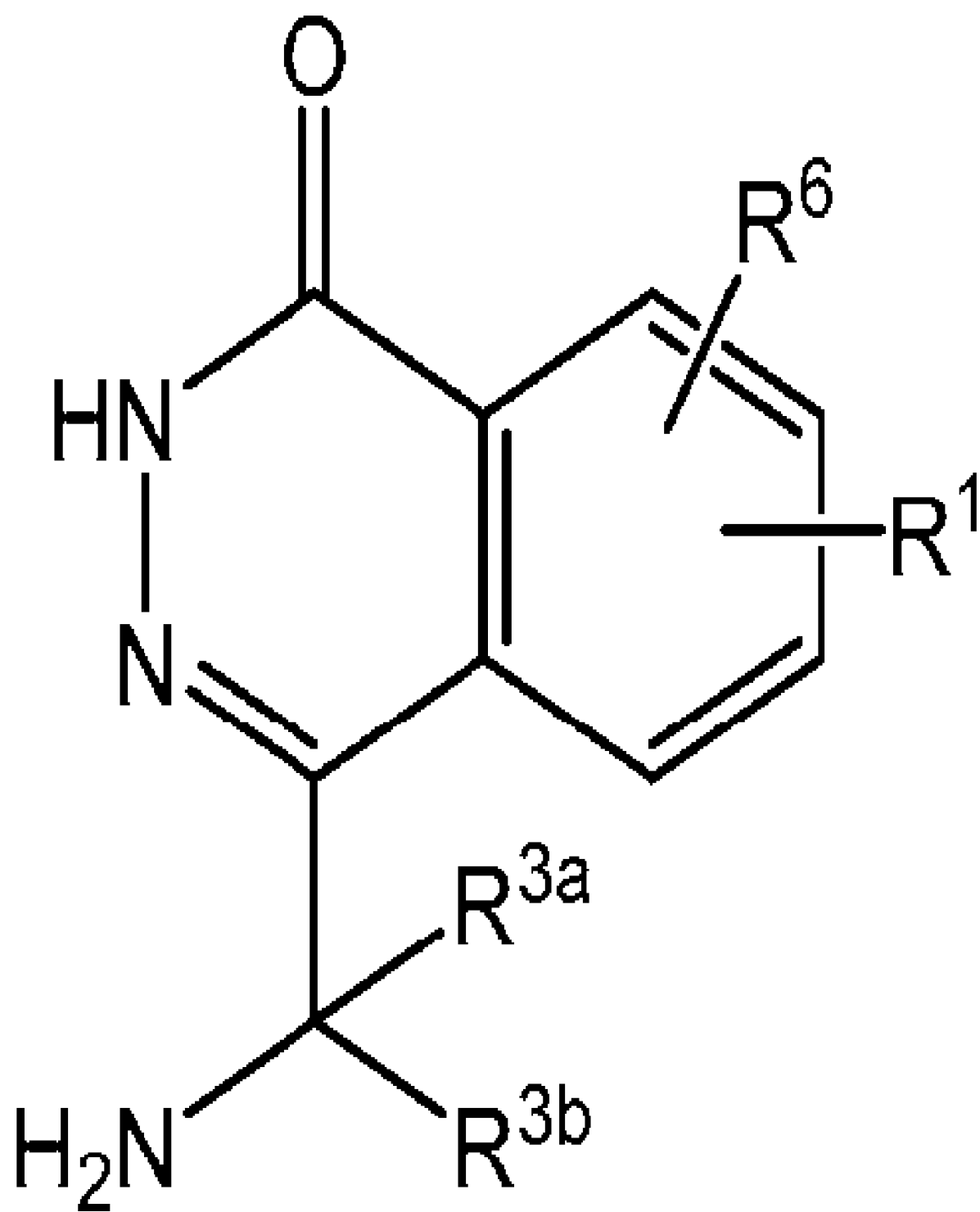
or a pharmaceutically acceptable salt thereof.

90. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
91. A method for inhibiting PRMT5 activity in a cell, comprising contacting the cell in which inhibition of PRMT5 activity is desired with an effective amount of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 90.
92. A method for treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents.
93. The method of claim 92, wherein the therapeutically effective amount of the compound is between about 0.01 to 300 mg/kg per day.
94. The method of claim 92, wherein the therapeutically effective amount of the compound is between about 0.1 to 100 g/kg per day.
95. The method according to any one of claims 91-94, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors,

Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

96. The method according to any one of claims 91-95, wherein the cancer is a MTAP-associated cancer.

97. The method of claim 95, wherein the cancer is hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, or head and neck cancer.



Formula (I)