

ESTROGEN RECEPTOR MODULATORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/613,442 entitled “ESTROGEN RECEPTOR MODULATORS AND USES THEREOF” filed on March 20, 2012, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, methods of making such compounds, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated.

BACKGROUND OF THE INVENTION

[0003] The estrogen receptor (“ER”) is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Endogenous estrogens include 17 β -estradiol and estrones. ER has been found to have two isoforms, ER- α and ER- β .

[0004] Estrogens and estrogen receptors are implicated in a number of diseases or conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as others diseases or conditions.

SUMMARY OF THE INVENTION

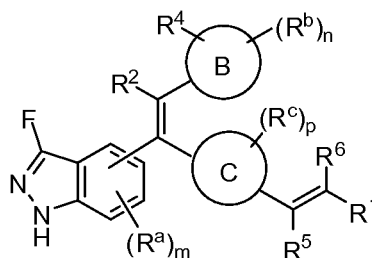
[0005] In one aspect, presented herein are compounds that diminish the effects of estrogens with estrogen receptors and/or lower the concentrations of estrogen receptors, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some embodiments, compounds disclosed herein are estrogen receptor degrader compounds.

[0006] In one aspect, the compound described herein, or a pharmaceutically acceptable salt, or N-oxide thereof, is useful for the treatment of ER-related diseases or conditions including, but not limited to, ER- α dysfunction associated with cancer (e.g. bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), leiomyoma (e.g. uterine leiomyoma), central nervous system (CNS) defects (e.g. alcoholism, migraine), cardiovascular system defects (e.g. aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis,

cardiovascular disease, coronary artery disease, hypertension), hematological system defects (e.g. deep vein thrombosis), immune and inflammation diseases (e.g. Graves' Disease, arthritis, multiple sclerosis, cirrhosis), susceptibility to infection (e.g. hepatitis B, chronic liver disease), metabolic defects (e.g. bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (e.g. Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (e.g. anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis) and reproductive defects (e.g. age of menarche, endometriosis, infertility).

[0007] In one aspect, described herein are compounds, pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein (e.g. compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and compounds in Table 1), are estrogen receptor modulators. In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or compounds in Table 1 are estrogen receptor antagonists. In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or compounds in Table 1 are estrogen receptor degraders. In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or compounds in Table 1 are estrogen receptor antagonists as well as estrogen receptor degraders. In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or compounds in Table 1 display minimal or no estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compounds of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) or compounds in Table 1 offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

[0008] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, metabolite or prodrug thereof:



Formula (I)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

R^2 is C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 deuteroalkyl, or C_3-C_6 cycloalkyl;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$,

substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, and substituted or unsubstituted C_1-C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, -

$S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, -

OCO_2R^9 , $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, -

$NR^7C(=O)OR^9$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-

C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-

C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted

C_1-C_6 fluoroalkoxy, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted

phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1-C_6 alkyl, or C_1-

C_6 fluoroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, -

$S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1-

C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, or C_1-C_6 heteroalkyl;

R^5 is H, C_1-C_4 alkyl, or halogen;

R^6 is H, C_1-C_4 alkyl, or halogen;

R^7 is H, or C_1-C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1-C_6 alkyl,

substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl,

substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-

C_6 heteroalkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted

C_2-C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted

monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1-C_6 alkyl, substituted or

unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted

or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted

or unsubstituted benzyl;

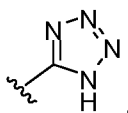
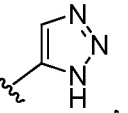
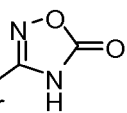
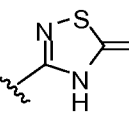
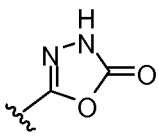
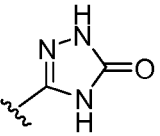
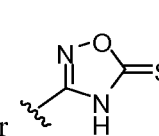
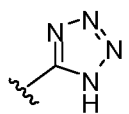
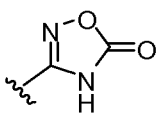
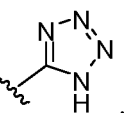
m is 0, 1, 2, or 3;

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

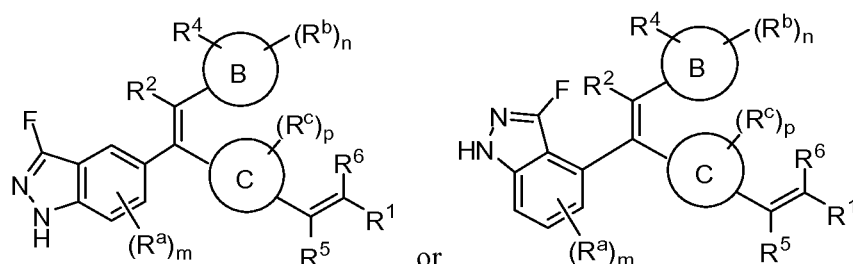
p is 0, 1, or 2;

provided that the compound is not (E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide; or (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

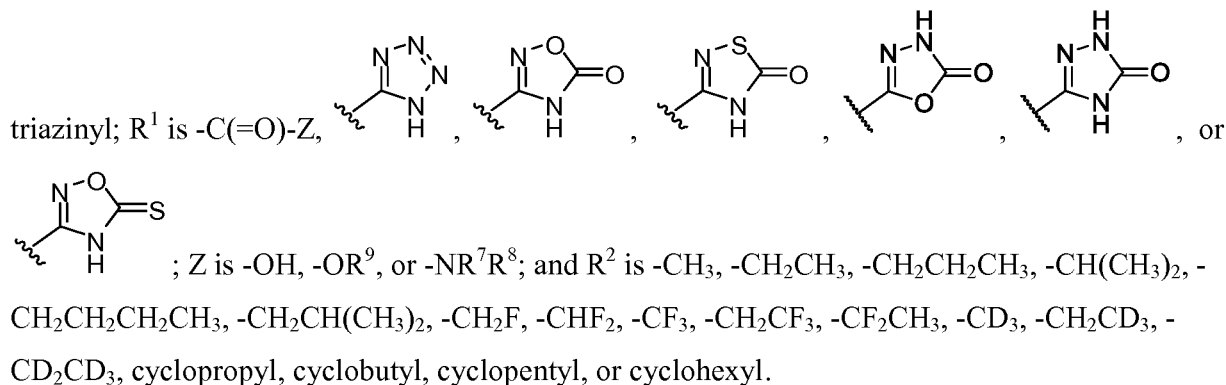
[0009] For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments, R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere. In other embodiments, R^1 is $-C(=O)-Z$. In some other embodiments, R^1 is a carboxylic acid bioisostere. In some embodiments, Z is $-OH$, $-OR^9$, $-NR^7R^8$, or $-NR^7S(=O)_2R^9$. In some embodiments, Z is $-OH$, $-OR^9$, or $-NR^7R^8$. In some embodiments, Z is $-OH$, or $-OR^9$. In some embodiments, Z is $-OH$.

[0010] In some embodiments, R^1 is $-C(=O)-Z$, , , , , , , or . In other embodiments, R^1 is $-C(=O)-Z$, , or . In other embodiments, R^1 is $-C(=O)-Z$, or .

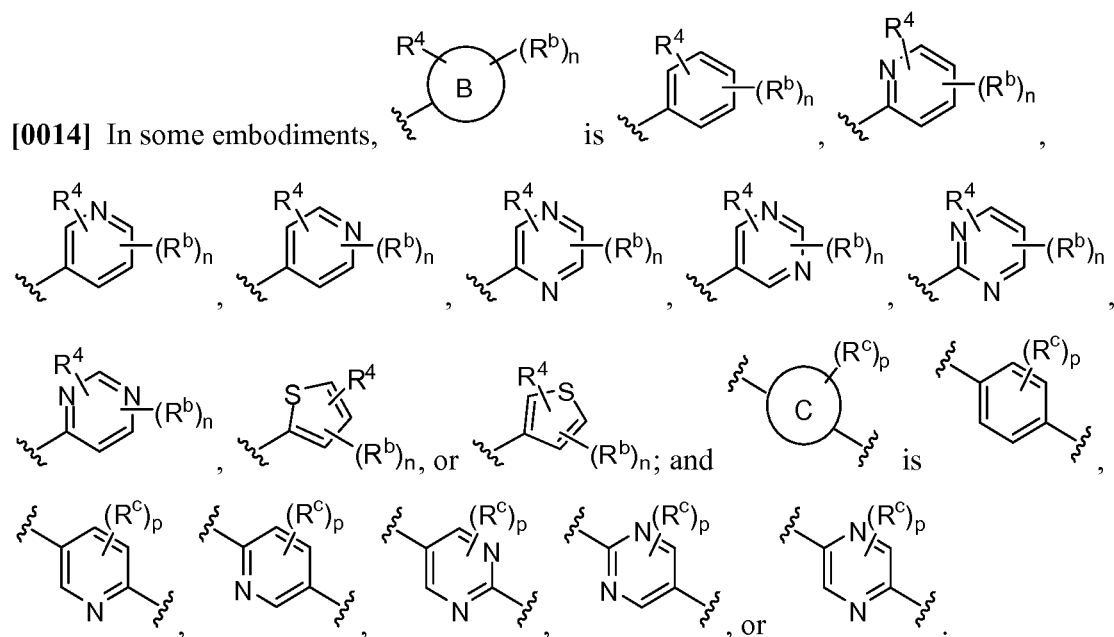
[0011] In some embodiments, the compound of Formula (I) has any one of the following structures:



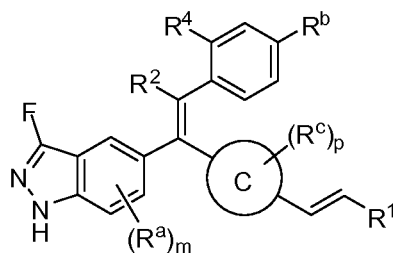
[0012] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



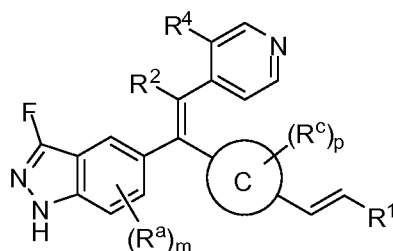
[0013] In some embodiments, ring B is phenyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl; and ring C is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl.



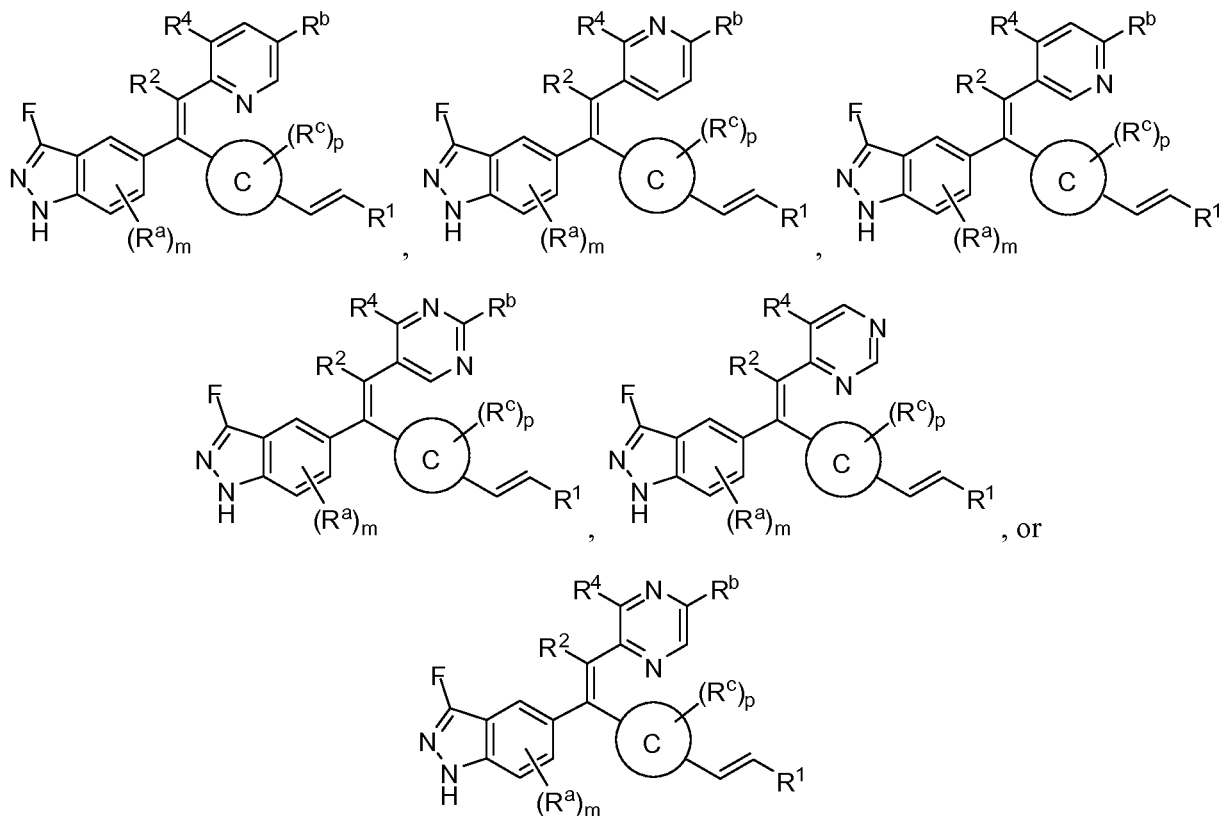
[0015] In some embodiments, the compound of Formula (I) has the following structure:



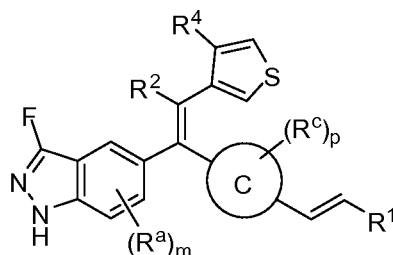
[0016] In some embodiments, the compound of Formula (I) has the following structure:



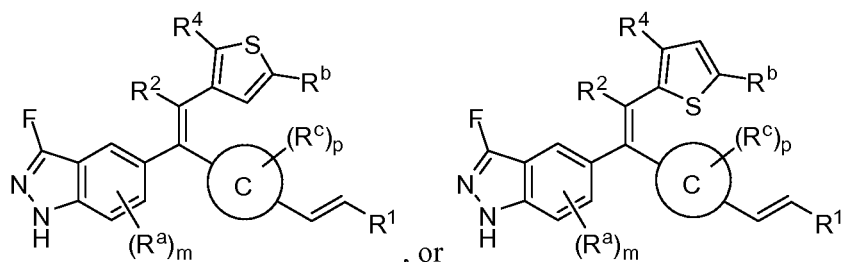
[0017] In some embodiments, the compound of Formula (I) has any one of the following structures:



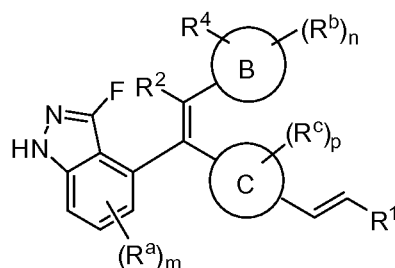
[0018] In some embodiments, the compound of Formula (I) has the following structure:



[0019] In some embodiments, the compound of Formula (I) has any one of the following structures:



[0020] In some embodiments, the compound of Formula (I) has the following structure:

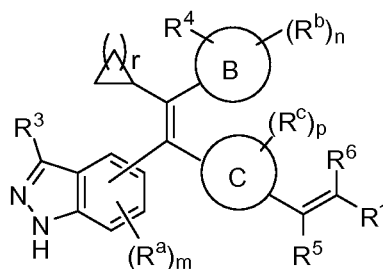


[0021] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[0022] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0023] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0024] In one aspect, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (II)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -

OCO_2R^9 , $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{NR}^7\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{NR}^7\text{C}(=\text{O})\text{R}^9$, $-\text{NR}^7\text{C}(=\text{O})\text{OR}^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl;

R^3 is H, halogen, $-\text{CN}$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^4 is H, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, $-\text{SR}^8$, $-\text{S}(=\text{O})\text{R}^9$, $-\text{S}(=\text{O})_2\text{R}^9$, $-\text{NHS}(=\text{O})_2\text{R}^9$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^9$, $-\text{OC}(=\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^8)_2$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^5 is H, C_1 - C_4 alkyl, or halogen;

R^6 is H, C_1 - C_4 alkyl, or halogen;

R^7 is H, or C_1 - C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

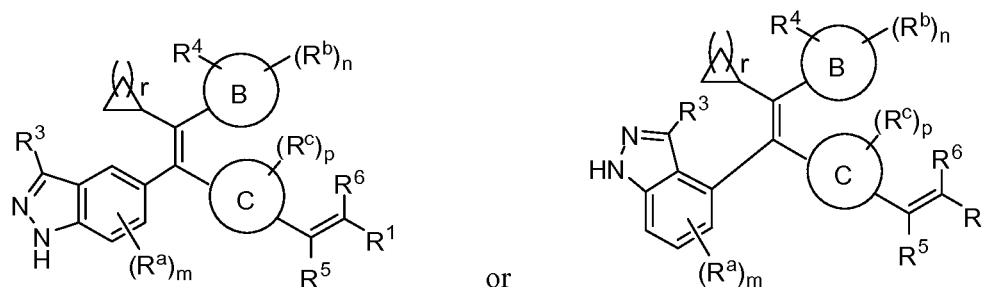
p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

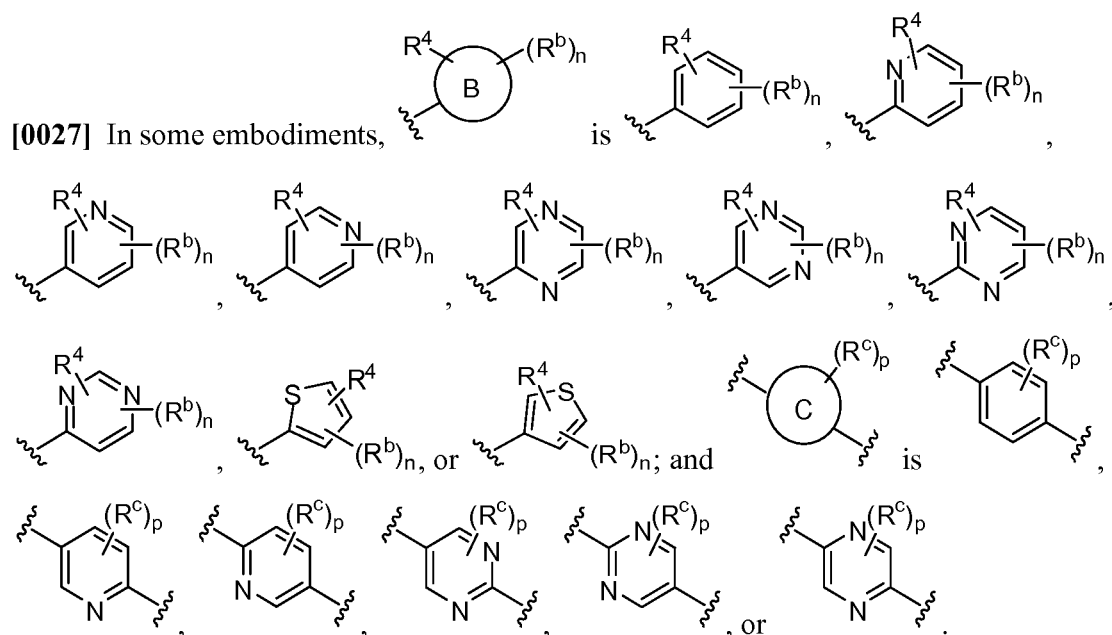
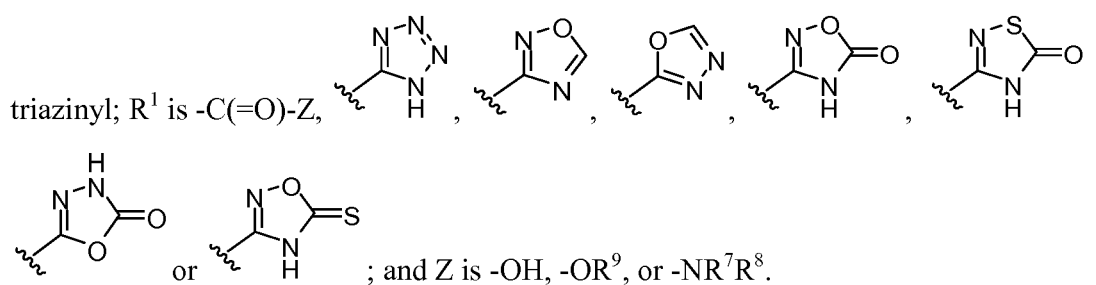
provided that the compound is not (E)-3-(4-((E)-2-Cyclopropyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(1H-indazol-4-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(1H-indazol-4-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(1H-indazol-4-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopentyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclohexyl-1-(1H-

indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyridin-2-yl)oxy)phenyl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1-methyl-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1-methyl-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide; or (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

[0025] In some embodiments, the compound of Formula (II) has any one of the following structures:



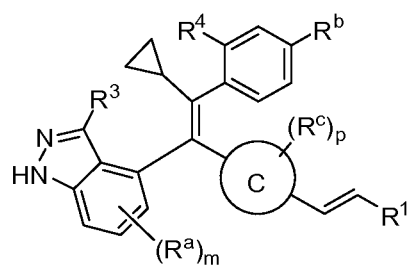
[0026] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



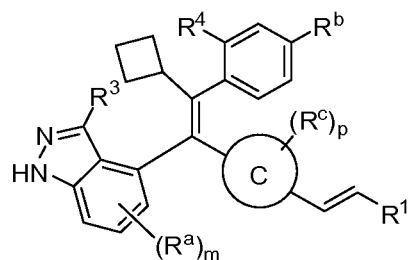
[0028] In some embodiments, r is 1.

[0029] In some embodiments, r is 2.

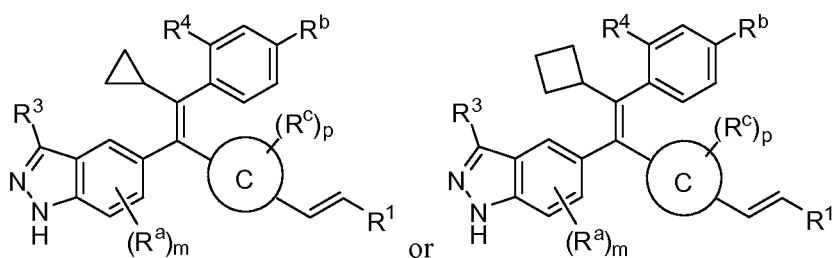
[0030] In some embodiments, the compound of Formula (II) has the following structure:



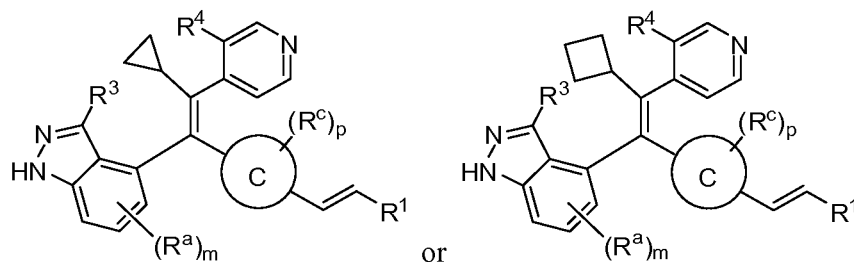
[0031] In some embodiments, the compound of Formula (II) has the following structure:



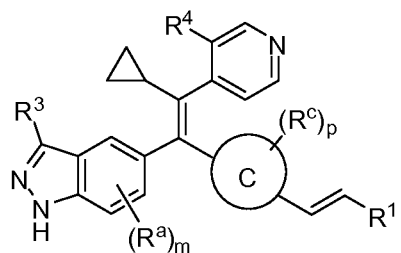
[0032] In some embodiments, the compound of Formula (II) has any one of the following structures:



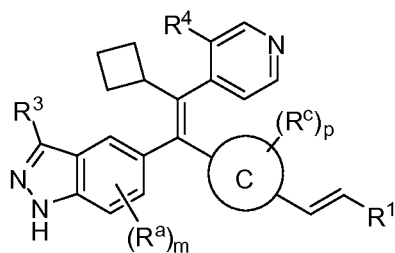
[0033] In some embodiments, the compound of Formula (II) has any one of the following structures:



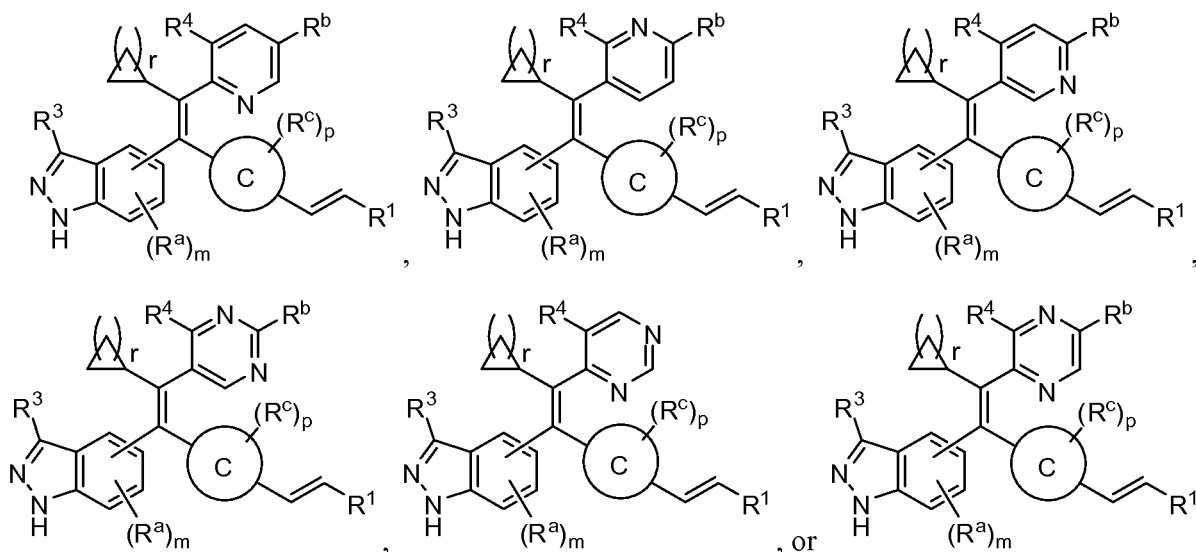
[0034] In some embodiments, the compound of Formula (II) has the following structure:



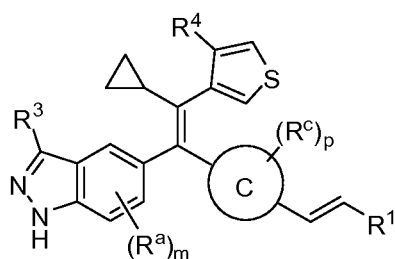
[0035] In some embodiments, the compound of Formula (II) has the following structure:



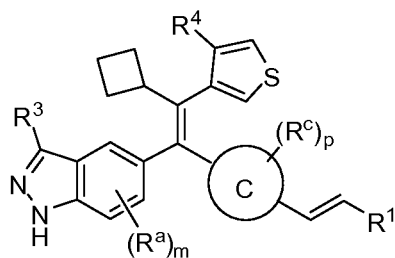
[0036] In some embodiments, the compound of Formula (II) has any one of the following structures:



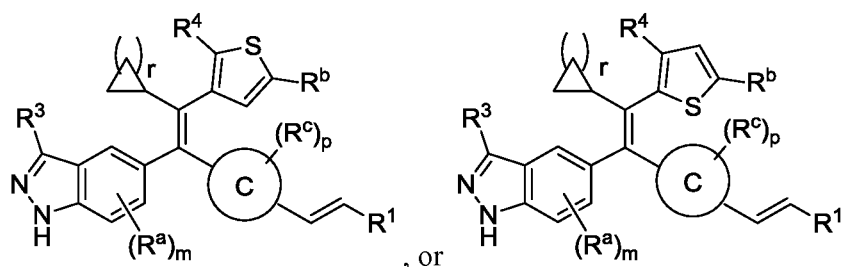
[0037] In some embodiments, the compound of Formula (II) has the following structure:



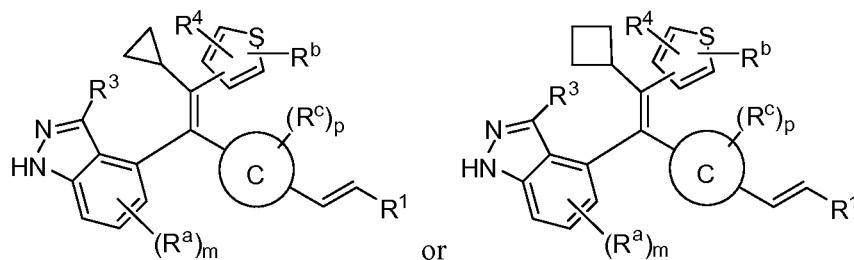
[0038] In some embodiments, the compound of Formula (II) has the following structure:



[0039] In some embodiments, the compound of Formula (II) has any one of the following structures:



[0040] In some embodiments, the compound of Formula (II) has any one of the following structures:

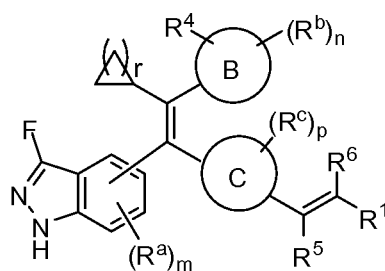


[0041] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[0042] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0043] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0044] In another aspect, described herein is compound of Formula (III), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (III)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$,

substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, and substituted or unsubstituted C_1-C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, -

$S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, -

OCO_2R^9 , $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, -

$NR^7C(=O)OR^9$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-

C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-

C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted

C_1-C_6 fluoroalkoxy, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted

phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1-C_6 alkyl, or C_1-

C_6 fluoroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, -

$S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1-

C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, or C_1-C_6 heteroalkyl;

R^5 is H, C_1-C_4 alkyl, or halogen;

R^6 is H, C_1-C_4 alkyl, or halogen;

R^7 is H, or C_1-C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1-C_6 alkyl,

substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl,

substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-

C_6 heteroalkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted

C_2-C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted

monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1-C_6 alkyl, substituted or

unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted

or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl,

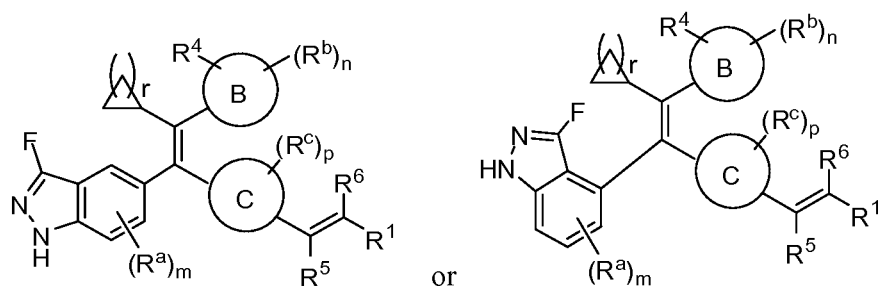
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted

or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

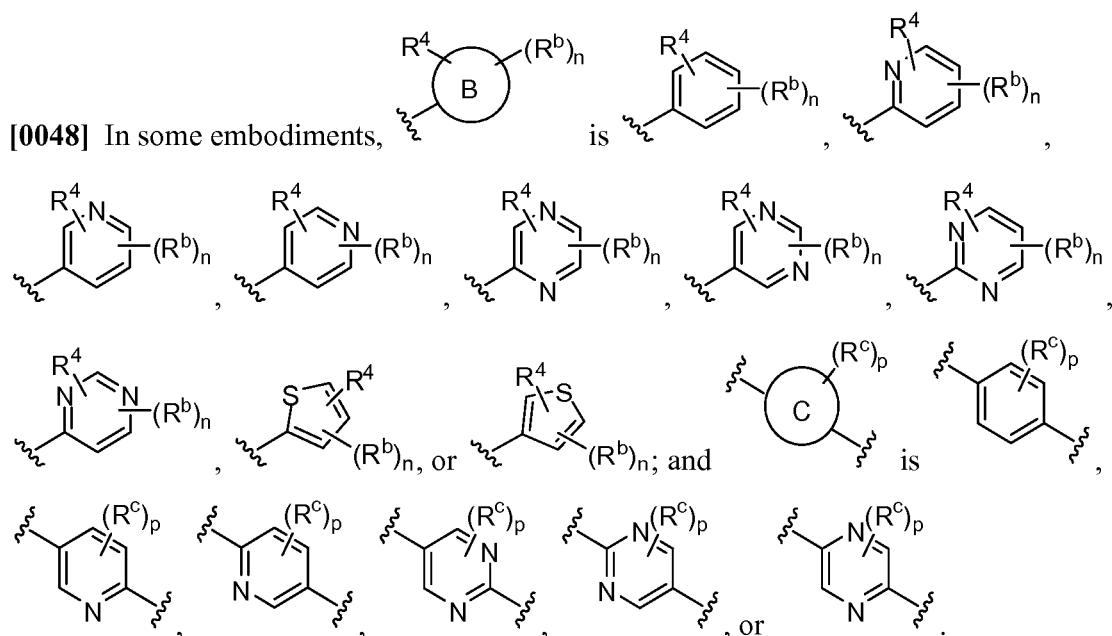
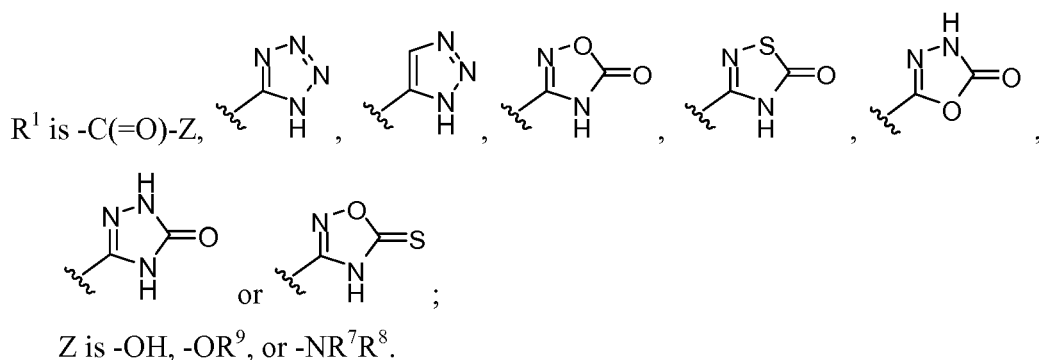
p is 0, 1, or 2; and



wherein:

ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl;

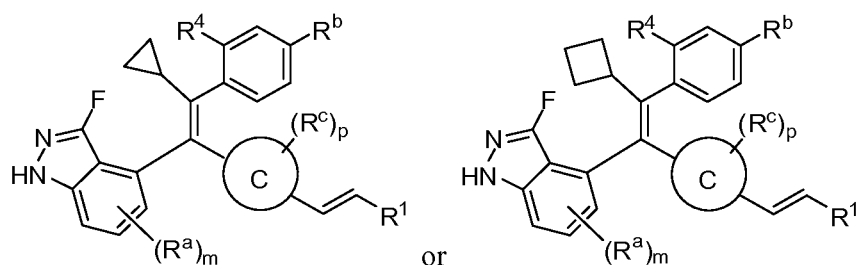
ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl;



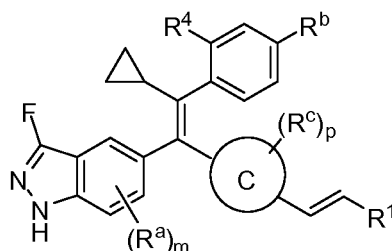
[0049] In some embodiments, r is 1.

[0050] In some embodiments, r is 2.

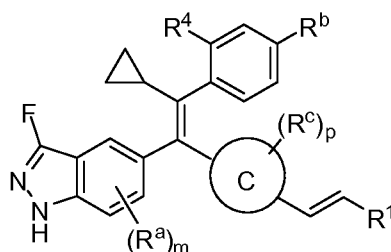
[0051] In some embodiments, the compound of Formula (III) has any one of the following structures:



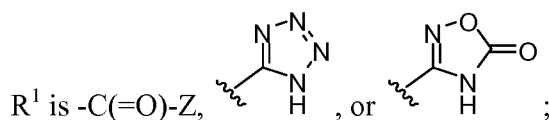
[0052] In some embodiments, the compound of Formula (III) has the following structure:



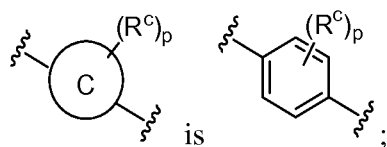
[0053] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is $-OH$;



R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

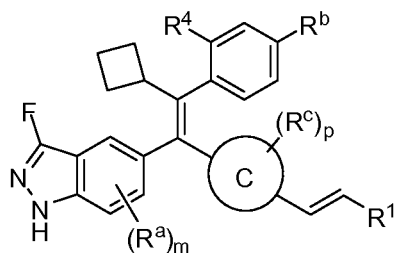
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

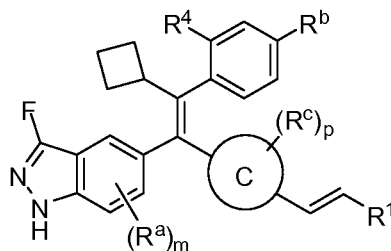
m is 0 or 1;

p is 0 or 1.

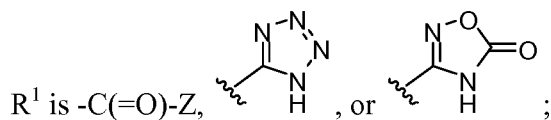
[0054] In some embodiments, the compound of Formula (III) has the following structure:



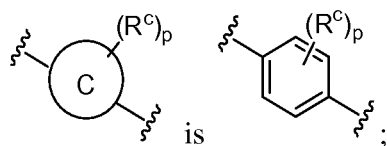
[0055] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is $-OH$;



R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

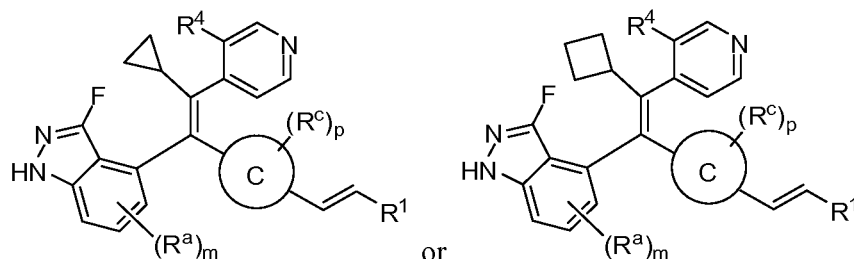
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

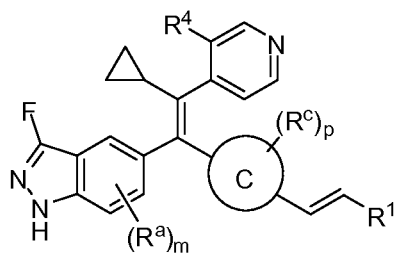
m is 0 or 1;

p is 0 or 1.

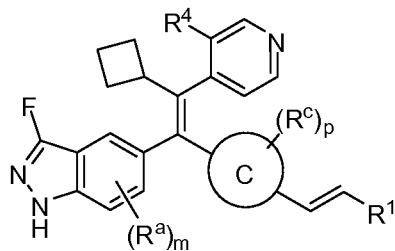
[0056] In some embodiments, the compound of Formula (III) has any one of the following structures:



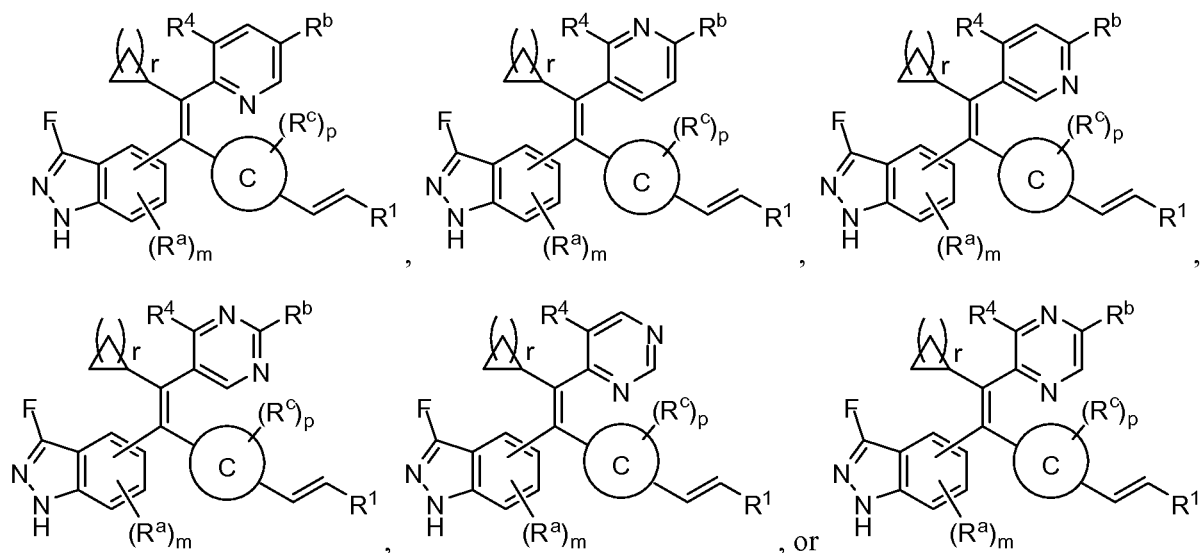
[0057] In some embodiments, the compound of Formula (III) has the following structure:



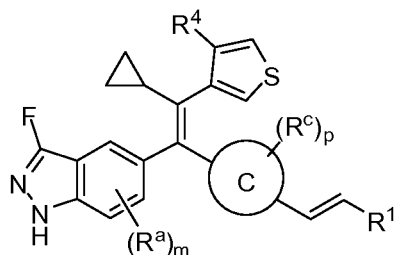
[0058] In some embodiments, the compound of Formula (III) has the following structure:



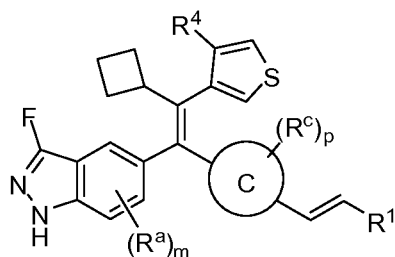
[0059] In some embodiments, the compound of Formula (III) has any one of the following structures:



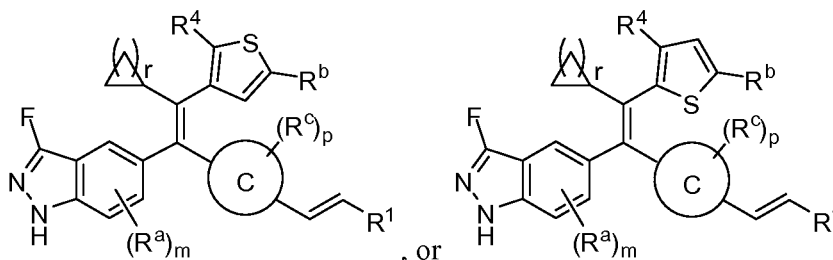
[0060] In some embodiments, the compound of Formula (III) has the following structure:



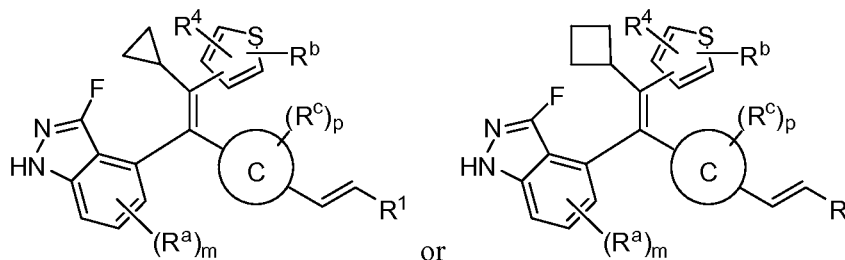
[0061] In some embodiments, the compound of Formula (III) has the following structure:



[0062] In some embodiments, the compound of Formula (III) has any one of the following structures:



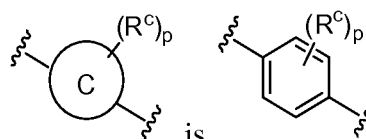
[0063] In some embodiments, the compound of Formula (III) has any one of the following structures:



[0064] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[0065] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0066] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

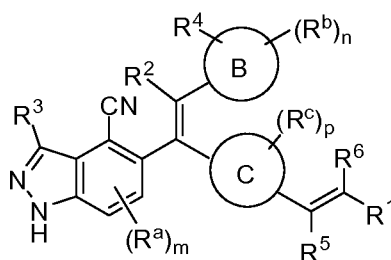


[0067] In some embodiments, R^a is H, F, Cl, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; R^c is H, F, Cl, -CN, -OH, -

OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl; R⁴ is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; m is 0 or 1; p is 0 or 1.

[0068] In some embodiments, R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃; R⁴ is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[0069] In yet another aspect, described herein is a compound of Formula (IV), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (IV)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

R² is C₁-C₆alkyl, C₁-C₆fluoroalkyl, C₁-C₆deuteroalkyl, or C₃-C₆cycloalkyl;

R³ is H, halogen, -CN, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R^4 is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^5 is H, C₁-C₄alkyl, or halogen;

R^6 is H, C₁-C₄alkyl, or halogen;

R^7 is H, or C₁-C₆alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

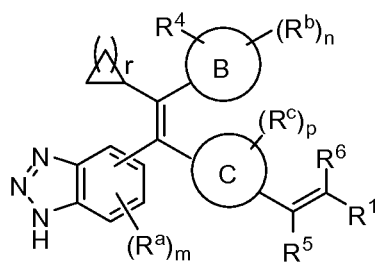
each R^9 is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, or 2;

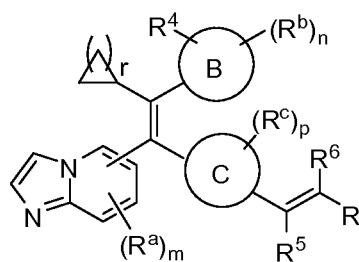
n is 0, 1, 2, or 3; and

p is 0, 1, or 2.

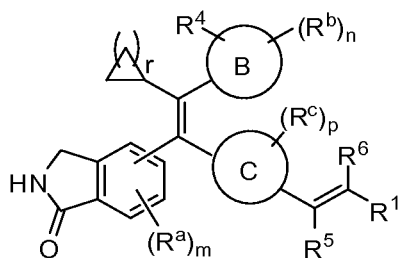
[0070] In an further aspect, described herein is a compound of Formula (V), Formula (VI), Formula (VII), Formula (VIII) or Formula (IX) or a pharmaceutically acceptable salt, or N-oxide thereof:



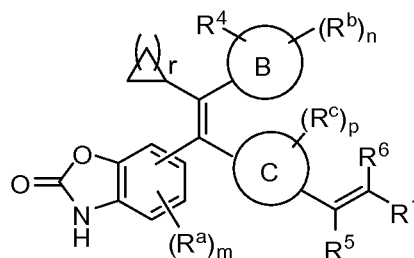
Formula (V)



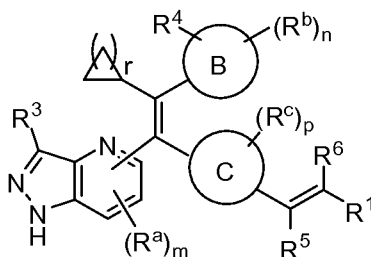
Formula (VI)



Formula (VII)



Formula (VIII)



Formula (IX)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R³ is H, halogen, -CN, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^4 is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^5 is H, C₁-C₄alkyl, or halogen;

R^6 is H, C₁-C₄alkyl, or halogen;

R^7 is H, or C₁-C₆alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

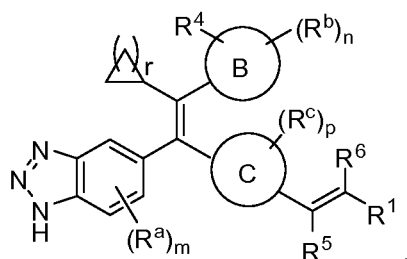
n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

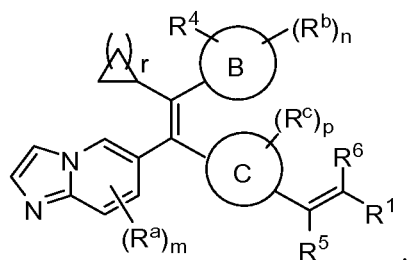
r is 1, 2, 3, or 4;

provided that the compound is not (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid.

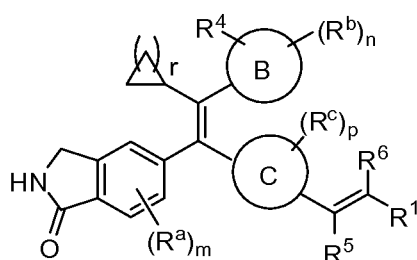
[0071] In some embodiments, the compound of Formula (V) has the following structure:



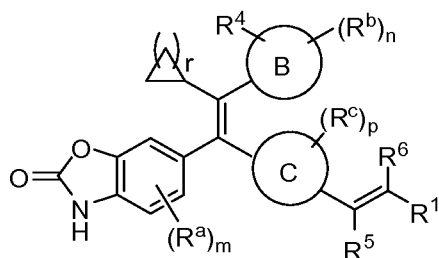
[0072] In some embodiments, the compound of Formula (VI) has the following structure:



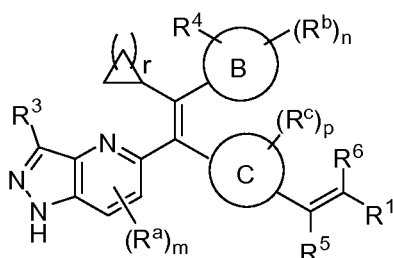
[0073] In some embodiments, the compound of Formula (VII) has the following structure:



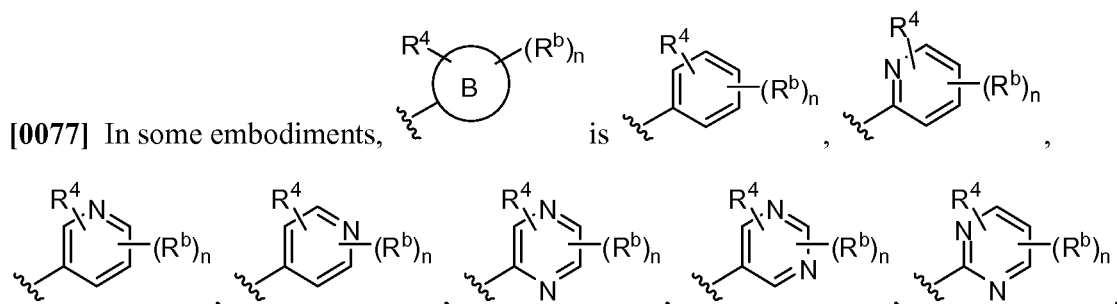
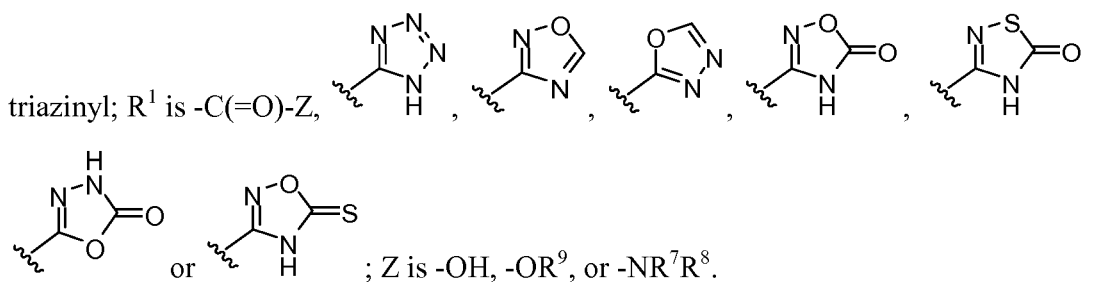
[0074] In some embodiments, the compound of Formula (VIII) has the following structure:

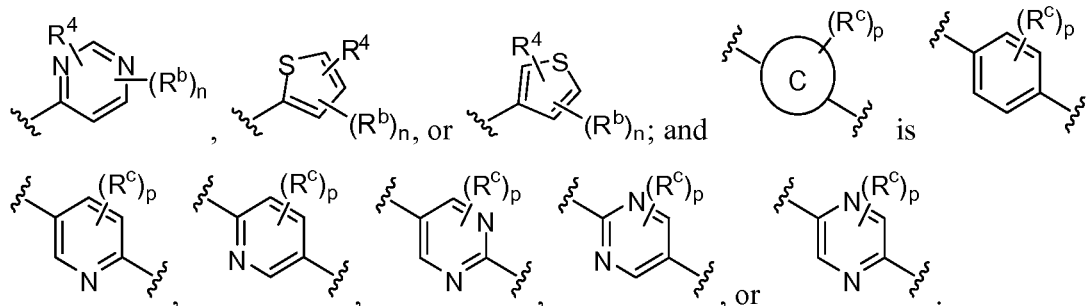


[0075] In some embodiments, the compound of Formula (IX) has the following structure:



[0076] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or





[0078] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

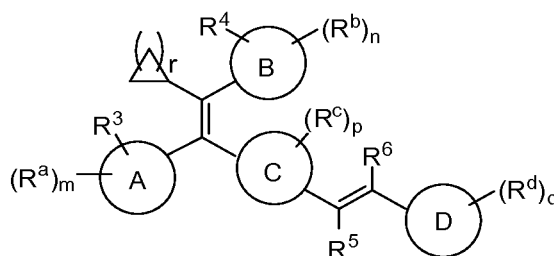
[0079] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[0080] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[0081] In some embodiments, r is 1.

[0082] In some embodiments, r is 2.

[0083] In another aspect, described herein is a compound of Formula (X), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (X)

wherein,

ring A is 8-, 9- or 10-membered bicyclic heteroaryl;

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or 6-membered monocyclic heteroaryl;

ring D is a 5-membered heterocycle or a 6-membered heterocycle;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸,

substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-

C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted

C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl;

each R^d is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

R^3 is H, halogen, $-CN$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^5 is H, C_1 - C_4 alkyl, or halogen;

R^6 is H, C_1 - C_4 alkyl, or halogen;

R^7 is H, or C_1 - C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

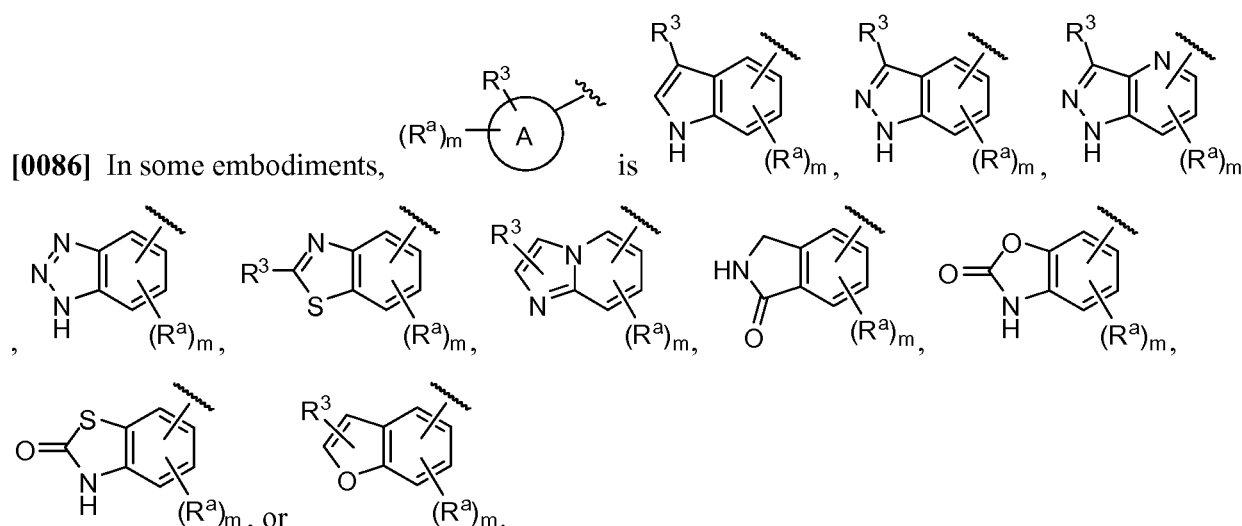
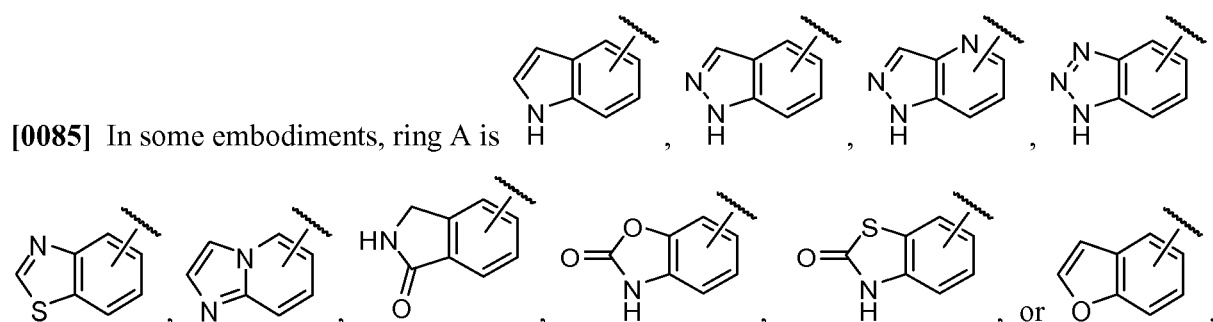
p is 0, 1, or 2;

q is 0, 1, 2, or 3; and

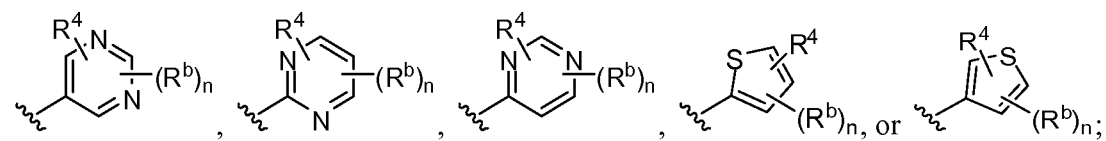
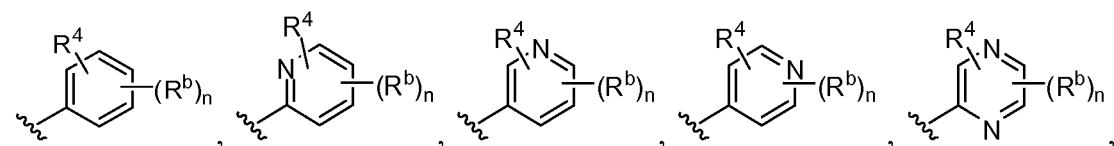
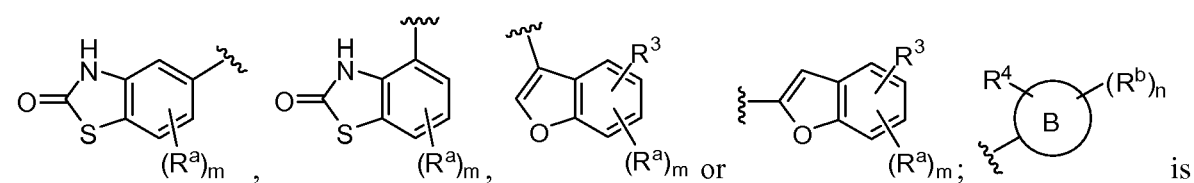
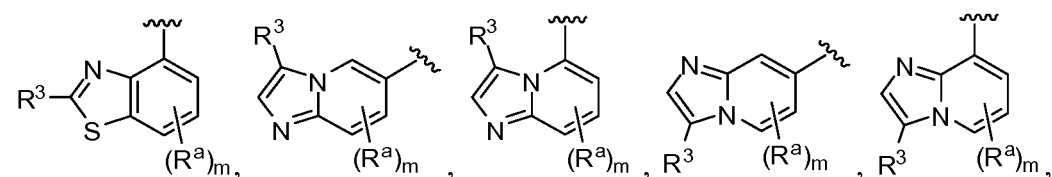
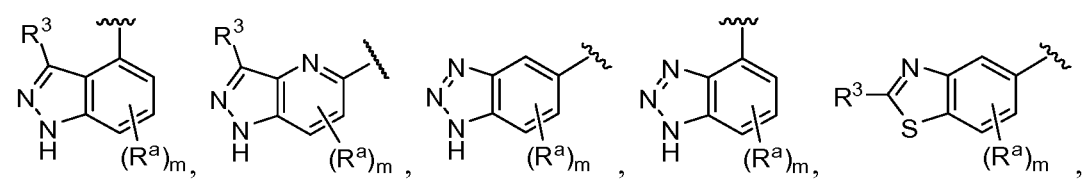
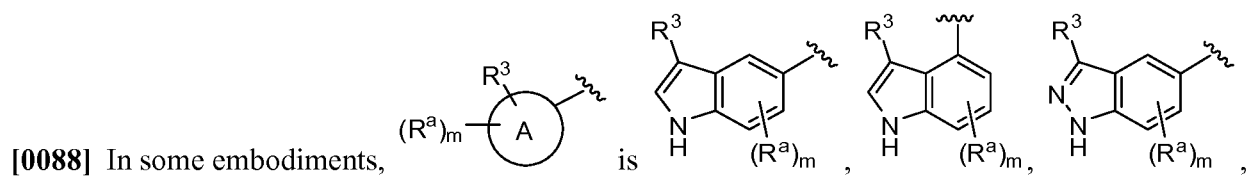
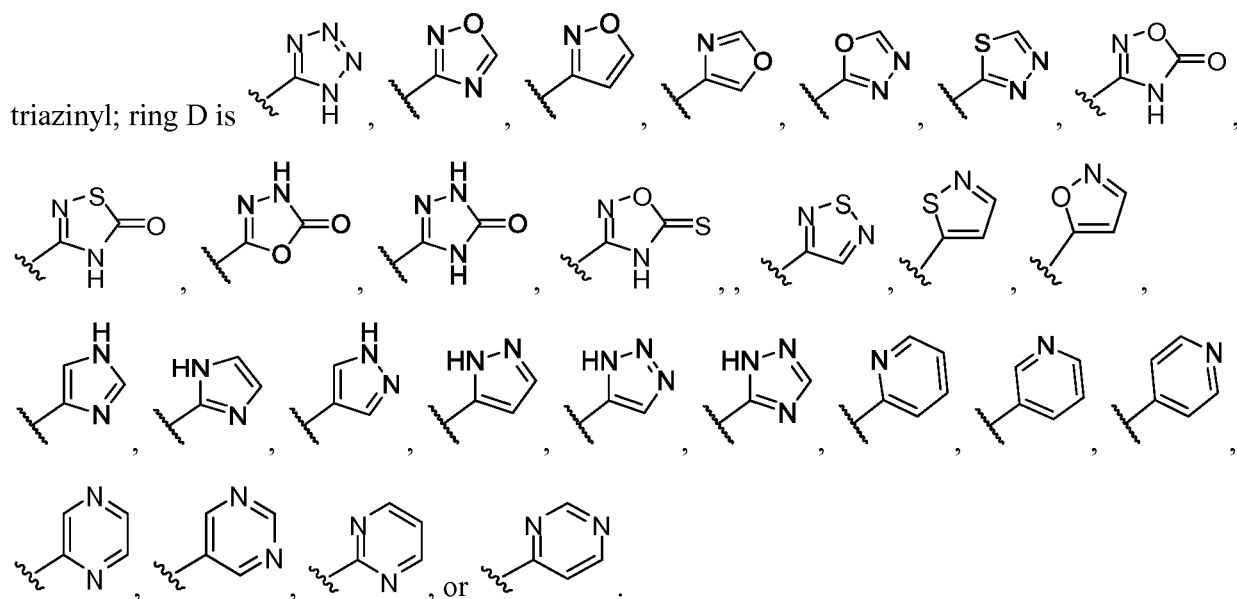
r is 1, 2, 3, or 4;

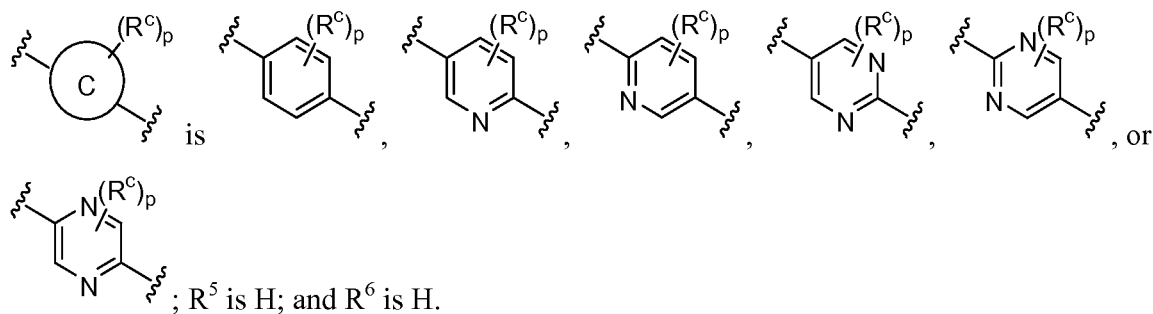
provided that the compound is not 5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)benzo[d]thiazole.

[0084] In some embodiments, ring A is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, indoliziny, azaindoliziny, indolyl, azaindolyl, indazolyl, azaindazolyl, benzimidazolyl, azabenzimidazolyl, benzotriazolyl, azabenzotriazolyl, benzoxazolyl, azabenzoxazolyl, benzisoxazolyl, azabenzisoxazolyl, benzofuranyl, azabenzofuranyl, benzothienyl, azabenzothienyl, benzothiazolyl, azabenzothiazolyl, or purinyl.



[0087] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or





[0089] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

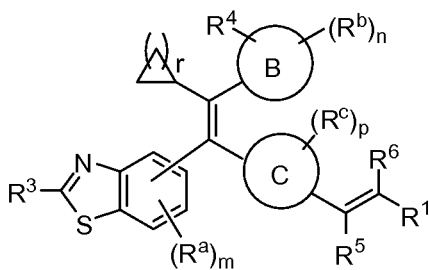
[0090] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[0091] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[0092] In some embodiments, r is 1.

[0093] In some embodiments, r is 2.

[0094] In yet a further aspect, described herein is a compound of Formula (XI), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (XI)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or 6-membered monocyclic heteroaryl;

R^1 is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

R^3 is H, halogen, -CN, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸,

substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-

C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R⁴ is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R⁵ is H, C₁-C₄alkyl, or halogen;

R⁶ is H, C₁-C₄alkyl, or halogen;

R⁷ is H, or C₁-C₆alkyl;

each R⁸ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R⁹ is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

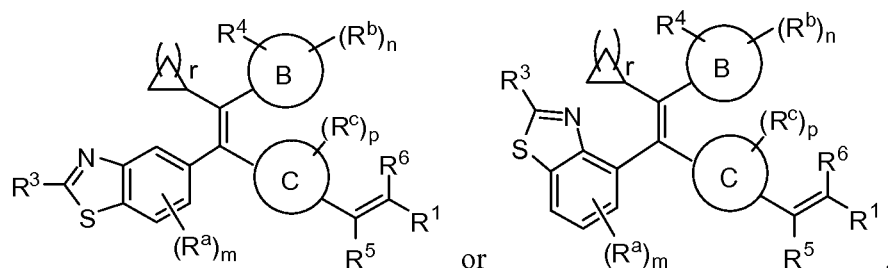
p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

provided that the compound is not (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-

(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid; or 5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)benzo[d]thiazole.

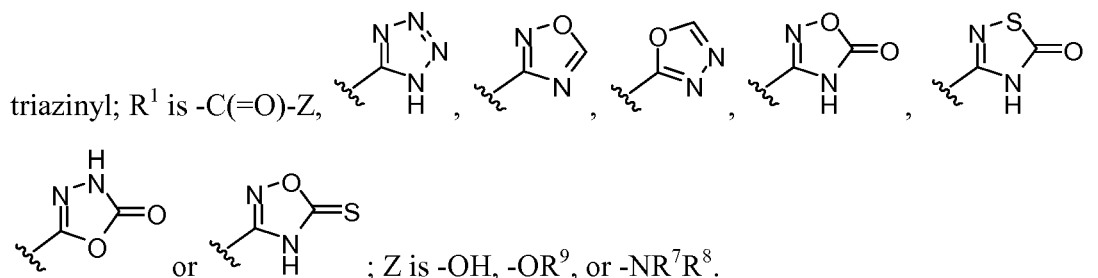
[0095] In some embodiments, the compound of Formula (XI) has any one of the following structures:



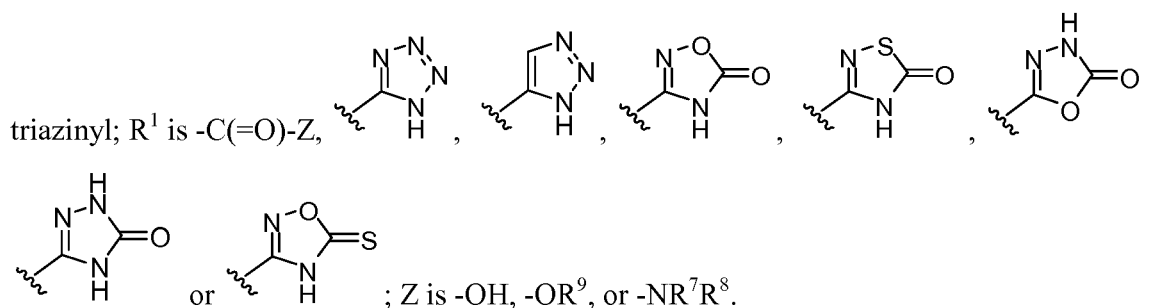
[0096] In some embodiments, r is 1.

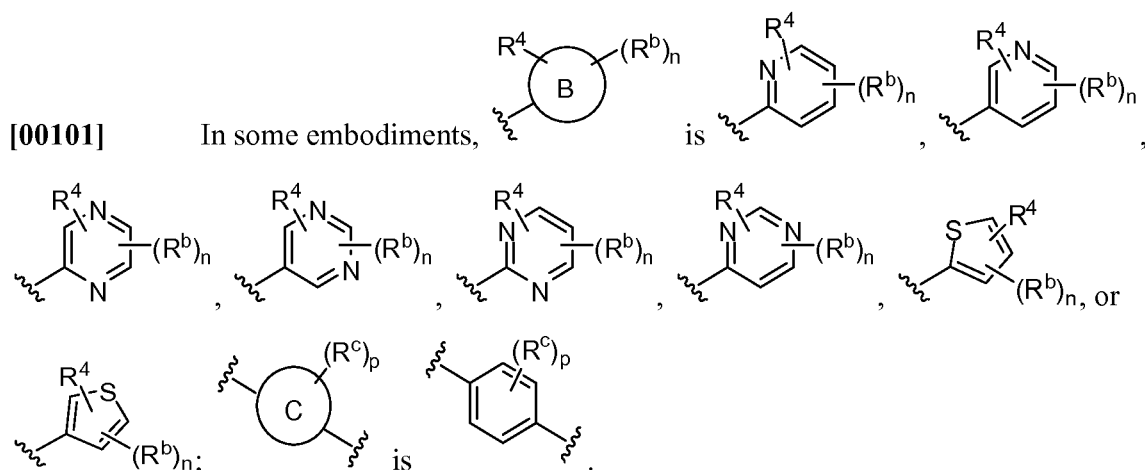
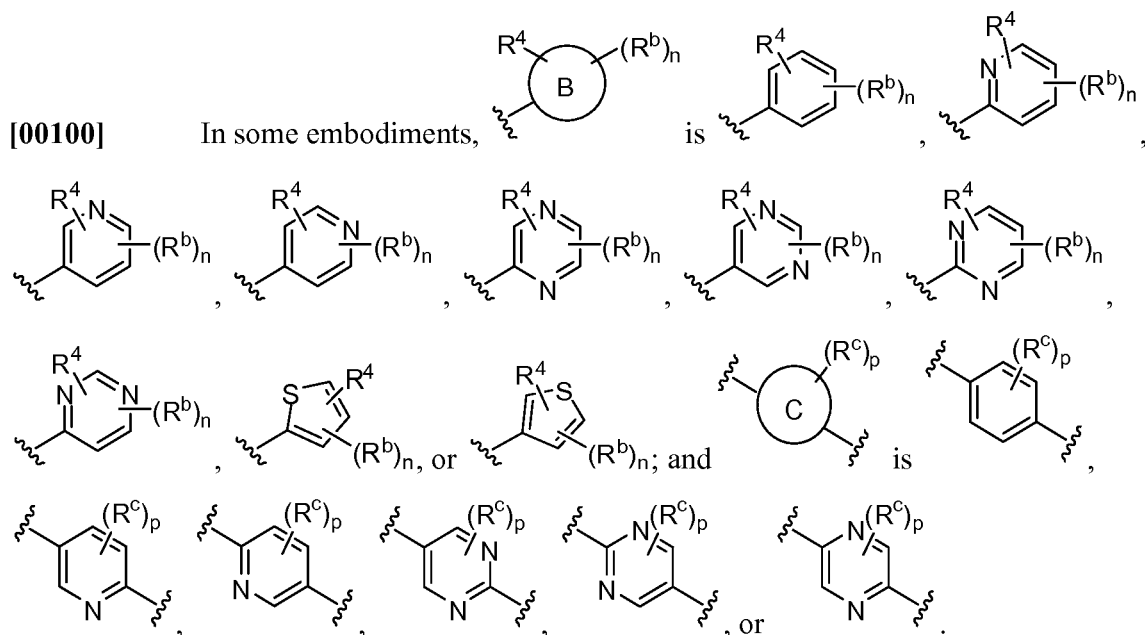
[0097] In some embodiments, r is 2.

[0098] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



[0099] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



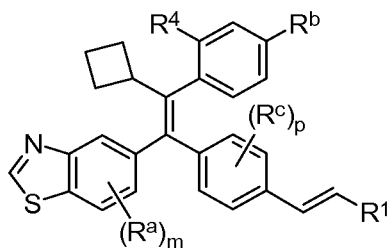


[00102] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

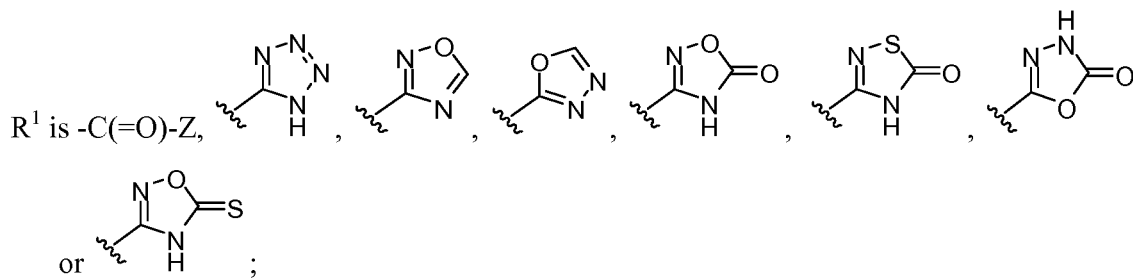
[00103] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[00104] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[00105] In some embodiments, the compound of Formula (XI) has the following structure, or a pharmaceutically acceptable salt, or N-oxide thereof:



wherein,



Z is -OH;

R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^b is Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃;

R⁴ is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

m is 0 or 1;

p is 0 or 1.

[00106] In some embodiments, compounds described herein include compounds in Table 1, or a pharmaceutically acceptable salt thereof.

[00107] Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[00108] Compounds disclosed herein are estrogen receptor modulators. In some embodiments, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and minimal or no ER agonist activity in uterine cells. In some embodiments, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

[00109] In some embodiments, compounds disclosed herein are estrogen receptor degraders. In some embodiments, compounds disclosed herein are estrogen receptor antagonists. In some embodiments, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

[00110] In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts or

prodrugs of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1).

[00111] Also described are pharmaceutical compositions comprising a therapeutically effective amount of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition also contains at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a suspension, a solution, an emulsion, an ointment, or a lotion.

[00112] In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutically active agents selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and aromatase inhibitors.

[00113] In some embodiments, provided herein is a method comprising administering a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, to a human with a disease or condition that is estrogen sensitive, estrogen receptor mediated or estrogen receptor dependent. In some embodiments, the human is already being administered one or more additional therapeutically active agents. In some embodiments, the method further comprises administering one or more additional therapeutically active agents other than a compound described herein, or a pharmaceutically acceptable salt thereof.

[00114] In some embodiments, the one or more additional therapeutically active agents other than a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, are selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, and aromatase inhibitors.

[00115] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used to treat hormone receptor positive metastatic breast cancer in a postmenopausal woman with disease progression following anti-estrogen therapy. In some embodiments, compounds are used to treat a hormonal dependent benign or malignant disease of the breast or reproductive tract in a mammal.

[00116] Pharmaceutical formulations described herein are administered to a mammal in a variety of ways, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00117] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered orally to a mammal. In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered systemically to a mammal. In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered intravenously to a mammal. In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered subcutaneously to a mammal.

[00118] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered topically to a mammal. In such embodiments, the compound, or a pharmaceutically acceptable salt thereof, is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, is administered topically to the skin of mammal.

[00119] In another aspect is the use of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder or conditions in which the activity of estrogen receptors contributes to the pathology and/or symptoms of the disease or condition. In one aspect, the disease or condition is any of the diseases or conditions specified herein.

[00120] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V),

(VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00121] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00122] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00123] Also provided is a method of reducing ER activation in a mammal comprising administering to the mammal a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the method comprises reducing ER activation in breast cells, ovarian cells, colon cells, prostate cells, endometrial cells, or uterine cells in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing the binding of estrogens to estrogen receptors in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing ER concentrations in the mammal.

[00124] In one aspect is the use of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, or uterine cancer. In some embodiments, the disease or condition is breast cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, or uterine cancer. In some embodiments, the disease or condition is described herein.

[00125] In some cases disclosed herein is the use of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is described herein.

[00126] In any of the embodiments disclosed herein, the mammal is a human.

[00127] In some embodiments, compounds provided herein are used to diminish, reduce, or eliminate the activity of estrogen receptors.

[00128] Articles of manufacture, which include: packaging material; a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1, or pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, within the packaging material; and a label that indicates that the compound or pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, is used for reducing, diminishing or eliminating the effects of estrogen receptors, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from a reduction or elimination of estrogen receptor activity, are provided.

[00129] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description

DETAILED DESCRIPTION OF THE INVENTION

[00130] Estrogen receptor alpha (ER- α ; NR3A1) and estrogen receptor beta (ER- β ; NR3A2) are steroid hormone receptors, which are members of the large nuclear receptor superfamily. Nuclear receptors share a common modular structure, which minimally includes a DNA binding domain (DBD) and a ligand binding domain (LBD). Steroid hormone receptors are soluble, intracellular proteins that act as ligand-regulated transcription factors. Vertebrates contain five closely related steroid hormone receptors (estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor, mineralocorticoid receptor), which regulate a wide spectrum of reproductive, metabolic and developmental activities. The activities of ER are controlled by the binding of endogenous estrogens, including 17 β -estradiol and estrones.

[00131] The ER- α gene is located on 6q25.1 and encodes a 595 AA protein. The ER- β gene resides on chromosome 14q23.3 and produces a 530 AA protein. However, due to alternative splicing and translation start sites, each of these genes can give rise to multiple isoforms. In addition

to the DNA binding domain (called C domain) and ligand binding domain (E domain) these receptors contain an N-terminal (A/B) domain, a hinge (D) domain that links the C and E domains, and a C-terminal extension (F domain) (Gronemeyer and Laudet; Protein Profile 2: 1173-1308, 1995). While the C and E domains of ER- α and ER- β are quite conserved (95% and 55% amino acid identity, respectively), conservation of the A/B, D and F domains is poor (below 30% amino acid identity). Both receptors are involved in the regulation and development of the female reproductive tract but also play various roles in the central nervous system, cardiovascular systems and bone metabolism.

[00132] The ligand binding pocket of steroid hormone receptors is deeply buried within the ligand binding domain. Upon binding, the ligand becomes part of the hydrophobic core of this domain. Consequently most steroid hormone receptors are instable in the absence of hormone and require assistance from chaperones, such as Hsp90, in order to maintain hormone-binding competency. The interaction with Hsp90 also controls nuclear translocation of these receptors. Ligand-binding stabilizes the receptor and initiates sequential conformational changes that release the chaperones, alter the interactions between the various receptor domains and remodel protein interaction surfaces that allow these receptors to translocate into the nucleus, bind DNA and engage in interactions with chromatin remodeling complexes and the transcriptional machinery. Although ER can interact with Hsp90, this interaction is not required for hormone binding and, dependent on the cellular context, apo-ER can be both cytoplasmic and nuclear. Biophysical studies indicated that DNA binding rather than ligand binding contributes to the stability of the receptor (Greenfield *et al.*, Biochemistry 40: 6646-6652, 2001).

[00133] ER can interact with DNA either directly by binding to a specific DNA sequence motif called estrogen response element (ERE) (classical pathway), or indirectly via protein-protein interactions (nonclassical pathway) (Welboren *et al.*, Endocrine-Related Cancer 16: 1073-1089, 2009). In the nonclassical pathway, ER has been shown to tether to other transcription factors including SP-1, AP-1 and NF- κ B. These interactions appear to play critical roles in the ability of ER to regulate cell proliferation and differentiation.

[00134] Both types of ER DNA interactions can result in gene activation or repression dependent on the transcriptional coregulators that are recruited by the respective ER-ERE complex (Klinge, Steroid 65: 227-251, 2000). The recruitment of coregulators is primarily mediated by two protein interaction surfaces, the AF2 and AF1. AF2 is located in the ER E-domain and its conformation is directly regulated by the ligand (Brzozowski *et al.*, Nature 389: 753-758, 1997). Full agonists appear to promote the recruitment of co-activators, whereas weak agonists and antagonists facilitate the binding of co-repressors. The regulation of protein with the AF1 is less well understood but can be controlled by serine phosphorylation (Ward and Weigel, Biofactors 35: 528-536, 2009). One of the involved phosphorylation sites (S118) appears to control the transcriptional activity of ER

in the presence of antagonists such as tamoxifen, which plays an important role in the treatment of breast cancer. While full agonists appear to arrest ER in certain conformation, weak agonists tend to maintain ER in equilibrium between different conformations, allowing cell-dependent differences in co-regulator repertoires to modulate the activity of ER in a cell-dependent manner (Tamrazi *et al.*, Mol. Endocrinol. 17: 2593-2602, 2003). Interactions of ER with DNA are dynamic and include, but are not limited to, the degradation of ER by the proteasome (Reid *et al.*, Mol Cell 11: 695-707, 2003). The degradation of ER with ligands provides an attractive treatment strategy for disease or conditions that estrogen-sensitive and/or resistant to available anti-hormonal treatments.

[00135] ER signaling is crucial for the development and maintenance of female reproductive organs including breasts, ovulation and thickening of the endometrium. ER signaling also has a role in bone mass, lipid metabolism, cancers, etc. About 70% of breast cancers express ER- α (ER- α positive) and are dependent on estrogens for growth and survival. Other cancers also are thought to be dependent on ER- α signaling for growth and survival, such as for example ovarian and endometrial cancers. The ER- α antagonist tamoxifen has been used to treat early and advanced ER- α positive breast cancer in both pre- and post-menopausal women. Fulvestrant (FaslodexTM) a steroid-based ER antagonist is used to treat breast cancer in women which has have progressed despite therapy with tamoxifen. Steroidal and non-steroidal aromatase inhibitors are also used to treat cancers in humans. In some embodiments, the steroidal and non-steroidal aromatase inhibitors block the production of estrogen from androstenedione and testosterone in post-menopausal women, thereby blocking ER dependent growth in the cancers. In addition to these anti-hormonal agents, progressive ER positive breast cancer is treated in some cases with a variety of other chemotherapeutics, such as for example, the anthracyclines, platins, taxanes. In some cases, ER positive breast cancers that harbor genetic amplification of the ERB-B/HER2 tyrosine kinase receptor are treated with the monoclonal antibody trastuzumab (HerceptinTM) or the small molecule pan-ERB-B inhibitor lapatinib. Despite this battery of anti-hormonal, chemotherapeutic and small-molecule and antibody-based targeted therapies, many women with ER- α positive breast develop progressive metastatic disease and are in need of new therapies. Importantly, the majority of ER positive tumors that progress on existing anti-hormonal, as well as and other therapies, are thought to remain dependent on ER- α for growth and survival. Thus, there is a need for new ER- α targeting agents that have activity in the setting of metastatic disease and acquired resistance.

[00136] In one aspect, described herein are compounds that are selective estrogen receptor modulators (SERMs). In specific embodiments, the SERMs described herein are selective estrogen receptor degraders (SERDs). In some embodiments, in cell-based assays the compounds described herein result in a reduction in steady state ER- α levels (i.e. ER degradation) and are useful in the treatment of estrogen sensitive diseases or conditions and/or diseases or conditions that have

developed resistant to anti-hormonal therapies. In some embodiments, compounds disclosed herein minimize levels of the estrogen receptor in the nucleus.

[00137] Given the central role of ER- α in breast cancer development and progression, compounds disclosed herein are useful in the treatment of breast cancer, either alone or in combination with other agent agents that modulate other critical pathways in breast cancer, including but not limited to those that target IGF1R, EGFR, erB-B2 and 3 the PI3K/AKT/mTOR axis, HSP90, PARP or histone deacetylases.

[00138] Given the central role of ER- α in breast cancer development and progression, compounds disclosed herein are useful in the treatment of breast cancer, either alone or in combination with other agent used to treat breast cancer, including but not limited to aromatase inhibitors, anthracyclines, platins, nitrogen mustard alkylating agents, taxanes. Illustrative agent used to treat breast cancer, include, but are not limited to, paclitaxel, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, letrozole, gemcitabine, trastuzumab, pegfilgrastim, filgrastim, tamoxifen, docetaxel, toremifene, vinorelbine, capecitabine, ixabepilone, as well as others described herein.

[00139] ER-related diseases or conditions (for which the agents disclosed herein are therapeutically relevant) include ER- α dysfunction is also associated with cancer (bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), leiomyoma (uterine leiomyoma), central nervous system (CNS) defects (alcoholism, migraine), cardiovascular system defects (aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (deep vein thrombosis), immune and inflammation diseases (Graves' Disease, arthritis, multiple sclerosis, cirrhosis), susceptibility to infection (hepatitis B, chronic liver disease), metabolic defects (bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis) and reproductive defects (age of menarche, endometriosis, infertility).

[00140] In some embodiments, compounds disclosed herein are used to treat cancer in a mammal. In some embodiments, the cancer is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, uterine cancer, cervical cancer or lung cancer. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, uterine cancer, cervical cancer or lung cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is a hormone dependent cancer. In some embodiments, the cancer is an estrogen receptor dependent cancer. In some embodiments, the cancer is an estrogen-sensitive cancer. In some embodiments, the cancer is resistant to anti-hormonal treatment. In some embodiments, the cancer is an estrogen-sensitive cancer or an estrogen receptor dependent cancer

that is resistant to anti-hormonal treatment. In some embodiments, anti-hormonal treatment includes treatment with at least one agent selected from tamoxifen, fulvestrant, steroidal aromatase inhibitors, and non-steroidal aromatase inhibitors-resistant.

[00141] In some embodiments, compounds disclosed herein are used to treat hormone receptor positive metastatic breast cancer in a postmenopausal woman with disease progression following anti-estrogen therapy.

[00142] In some embodiments, compounds disclosed herein are used to treat a hormonal dependent benign or malignant disease of the breast or reproductive tract in a mammal. In some embodiments, the benign or malignant disease is breast cancer.

[00143] In some embodiments, compounds disclosed herein are used to treat cancer in a mammal, wherein the mammal is chemotherapy-naïve.

[00144] In some embodiments, compounds disclosed herein are used to treat cancer in a mammal, wherein the mammal is being treated for cancer with at least one anti-cancer agent. In one embodiment, the cancer is a hormone refractory cancer.

[00145] In some embodiments, compounds disclosed herein are used in the treatment of endometriosis in a mammal.

[00146] In some embodiments, compounds disclosed herein are used in the treatment of leiomyoma in a mammal. In some embodiments, the leiomyoma is an uterine leiomyoma, esophageal leiomyoma, cutaneous leiomyoma or small bowel leiomyoma. In some embodiments, compounds disclosed herein are used in the treatment of fibroids in a mammal (e.g. uterine fibroids).

[00147] In some embodiments, compounds disclosed herein are used in the treatment of hot flashes in a mammal.

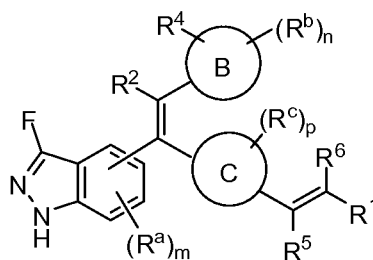
Compounds

[00148] Compounds described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, are estrogen receptor modulators. In specific embodiments, the compounds described herein are estrogen receptor degraders. In specific embodiments, the compounds described herein are estrogen receptor antagonists. In specific embodiments, the compounds described herein are estrogen receptor degraders and estrogen receptor antagonists with minimal or no estrogen receptor agonist activity.

[00149] In some embodiments, compounds disclosed herein are estrogen receptor degraders and estrogen receptor antagonists that exhibit: minimal or no estrogen receptor agonism; and/or anti-proliferative activity against breast cancer, ovarian cancer, endometrial cancer, cervical cancer cell lines; and/or maximal anti-proliferative efficacy against breast cancer, ovarian cancer, endometrial cancer, cervical cell lines in-vitro; and/or minimal agonism in the human endometrial (Ishikawa) cell

line; and/or no agonism in the human endometrial (Ishikawa) cell line; and/or minimal or no agonism in the immature rat uterine assay in-vivo; and/or inverse agonism in the immature rat uterine assay in-vivo; and/or anti-tumor activity in breast cancer, ovarian cancer, endometrial cancer, cervical cancer cell lines in xenograft assays in-vivo or other rodent models of these cancers.

[00150] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, metabolite or prodrug thereof:



Formula (I)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

R² is C₁-C₆alkyl, C₁-C₆fluoroalkyl, C₁-C₆deuteroalkyl, or C₃-C₆cycloalkyl;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R^4 is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^5 is H, C₁-C₄alkyl, or halogen;

R^6 is H, C₁-C₄alkyl, or halogen;

R^7 is H, or C₁-C₆alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

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

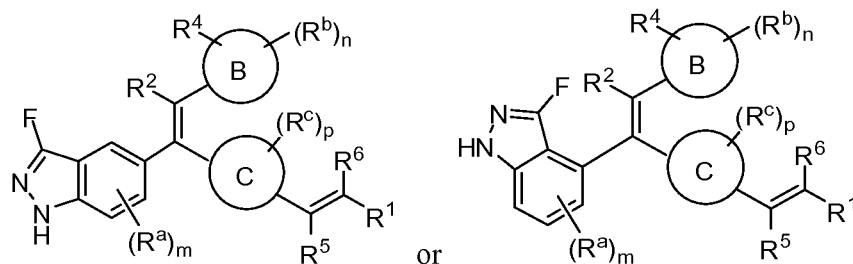
p is 0, 1, or 2;

provided that the compound is not (E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide; or (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

[00151] For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments, R^1 is -C(=O)-Z, or a carboxylic

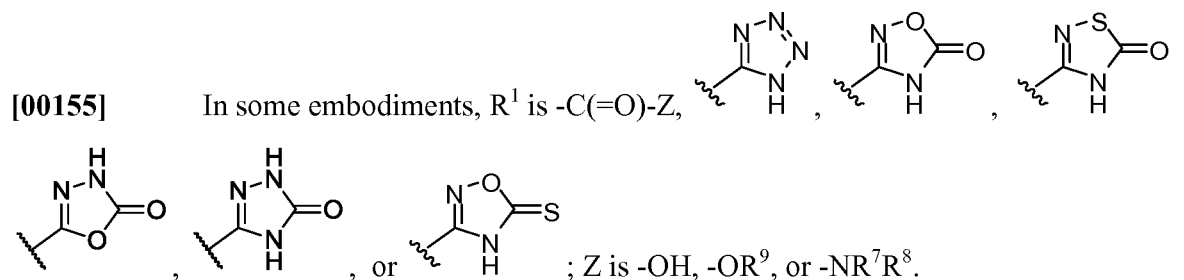
acid bioisostere. In other embodiments, R^1 is $-C(=O)-Z$. In some other embodiments, R^1 is a carboxylic acid bioisostere. In some embodiments, Z is $-OH$, $-OR^9$, $-NR^7R^8$, or $-NR^7S(=O)_2R^9$. In some embodiments, Z is $-OH$, $-OR^9$, or $-NR^7R^8$. In some embodiments, Z is $-OH$, or $-OR^9$. In some embodiments, Z is $-OH$.

[00152] In some embodiments, the compound of Formula (I) has any one of the following structures:



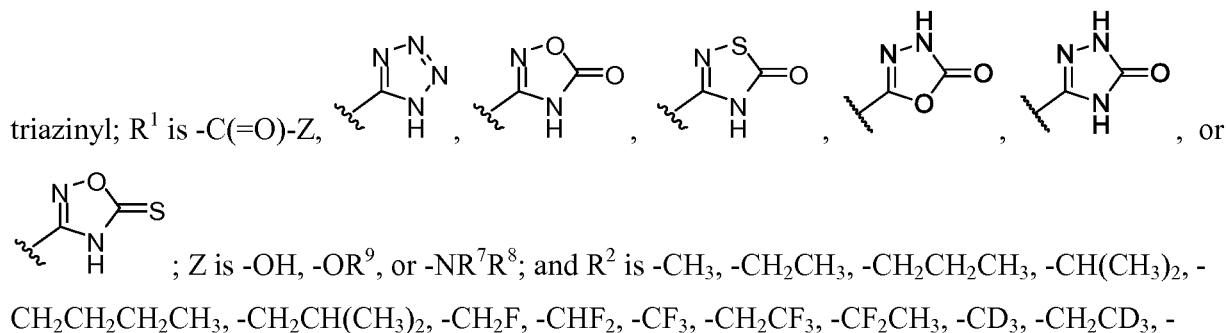
[00153] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00154] In some embodiments, ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl.

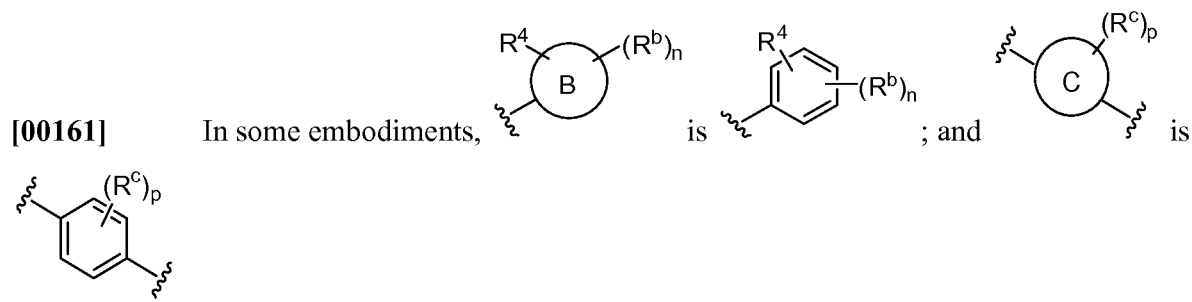
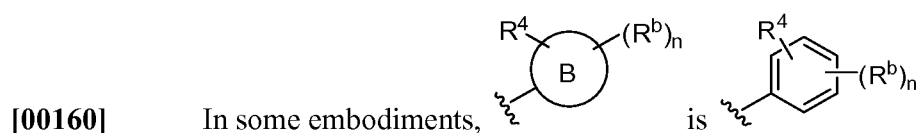
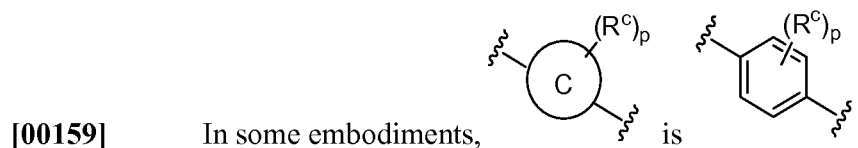
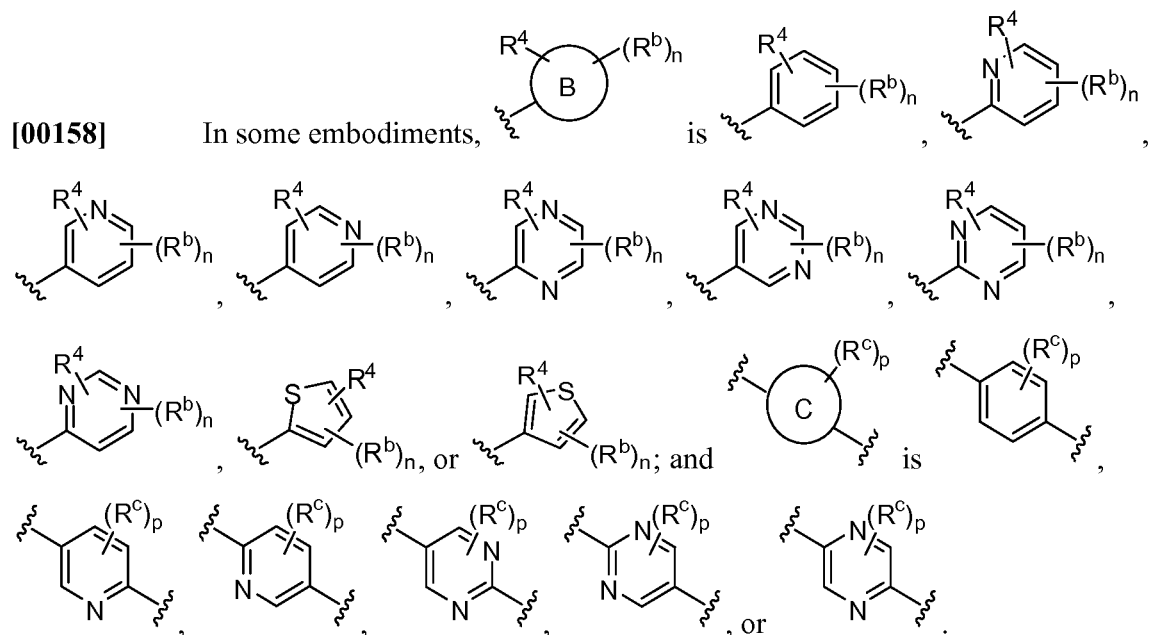


[00156] In some embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CD_3$, $-CH_2CD_3$, $-CD_2CD_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

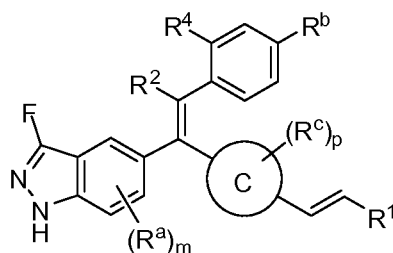
[00157] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



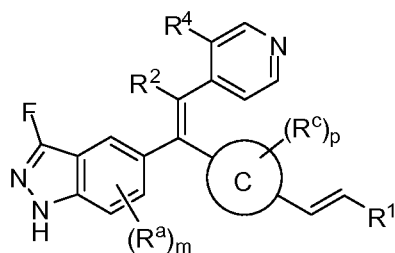
CD_2CD_3 , cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, ring B is phenyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl; and ring C is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl.



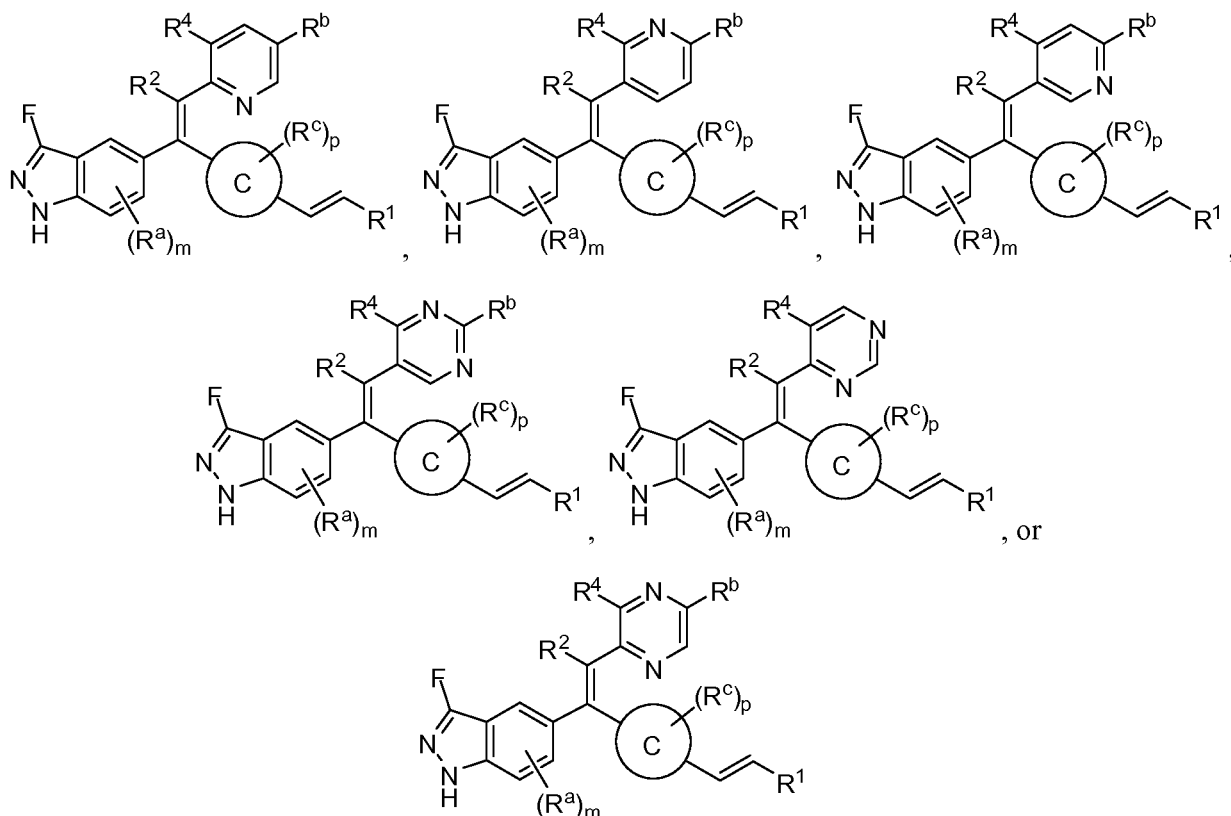
[00162] In some embodiments, the compound of Formula (I) has the following structure:



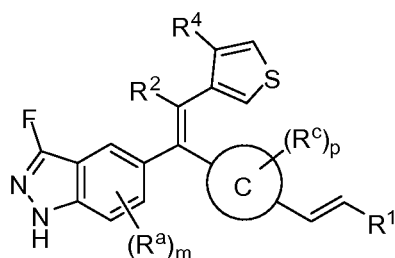
[00163] In some embodiments, the compound of Formula (I) has the following structure:



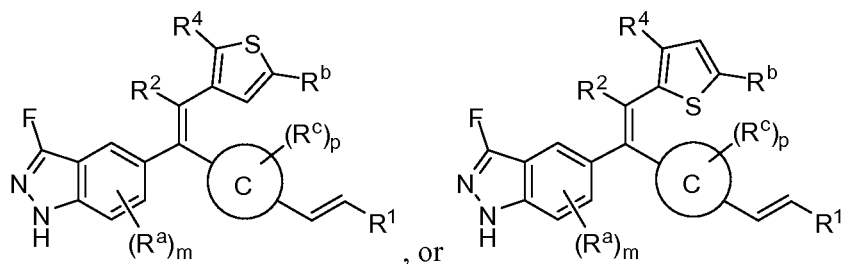
[00164] In some embodiments, the compound of Formula (I) has any one of the following structures:



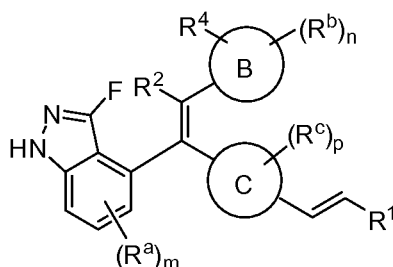
[00165] In some embodiments, the compound of Formula (I) has the following structure:



[00166] In some embodiments, the compound of Formula (I) has any one of the following structures:



[00167] In some embodiments, the compound of Formula (I) has the following structure:



[00168] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl. In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00169] In some embodiments, R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl. In some embodiments, R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00170] In some embodiments, each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, C₁-C₆alkyl, C₁-C₆fluoroalkyl, and C₁-C₆heteroalkyl. In some embodiments, each R^a is independently selected from H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, and -CH₂OH. In some embodiments, each R^a is independently selected from H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, and -CF₃.

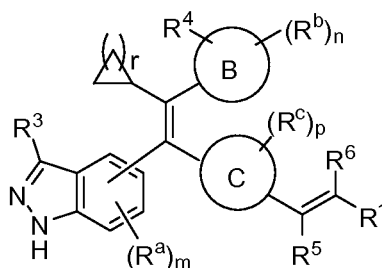
[00171] In some embodiments, each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl. In some embodiments, each R^c is independently selected from H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, and -CF₃.

[00172] In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0.

[00173] In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2.

[00174] In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0.

[00175] In one aspect, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (II)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, and substituted or unsubstituted C_1 - C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl;

R^3 is H, halogen, $-CN$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^5 is H, C_1 - C_4 alkyl, or halogen;

R^6 is H, C_1 - C_4 alkyl, or halogen;

R^7 is H, or C_1 - C_6 alkyl;

each R⁸ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R⁹ is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

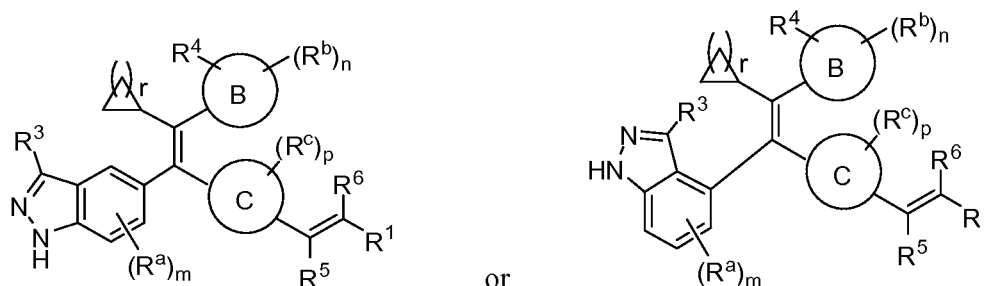
p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

provided that the compound is not (E)-3-(4-((E)-2-Cyclopropyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(1H-indazol-4-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(1H-indazol-4-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(1H-indazol-4-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopentyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclohexyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyridin-2-yl)oxy)phenyl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-

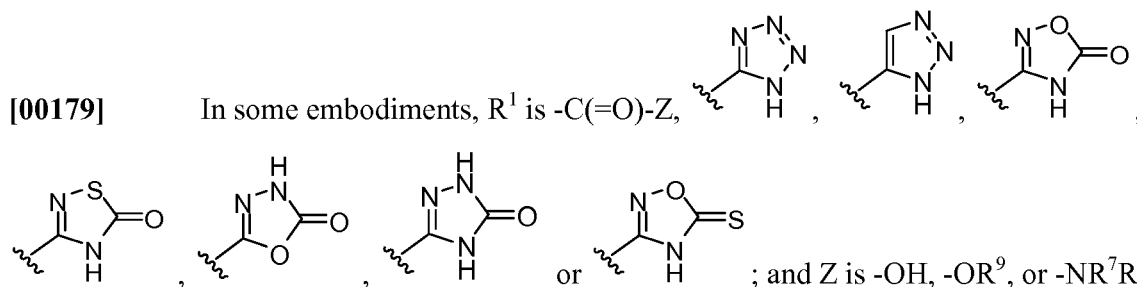
(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1-methyl-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1-methyl-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide; or (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

[00176] In some embodiments, the compound of Formula (II) has any one of the following structures:



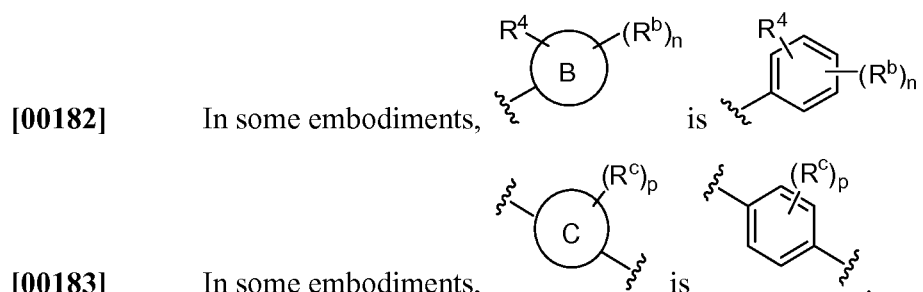
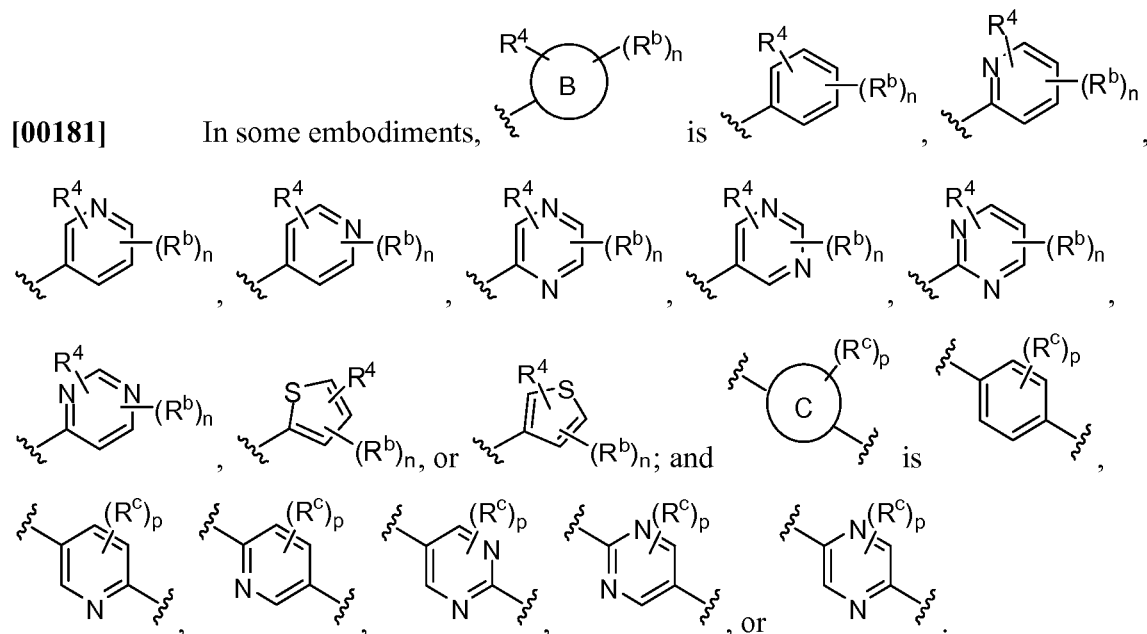
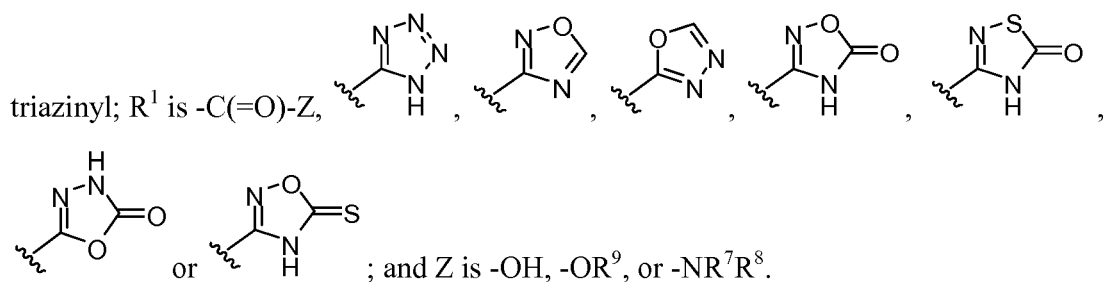
[00177] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00178] In some embodiments, ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl.



[00180] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl,

thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or

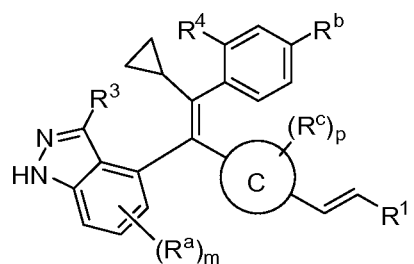


[00183] In some embodiments,

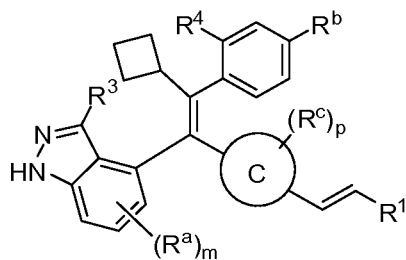
[00184] In some embodiments, r is 1.

[00185] In some embodiments, r is 2.

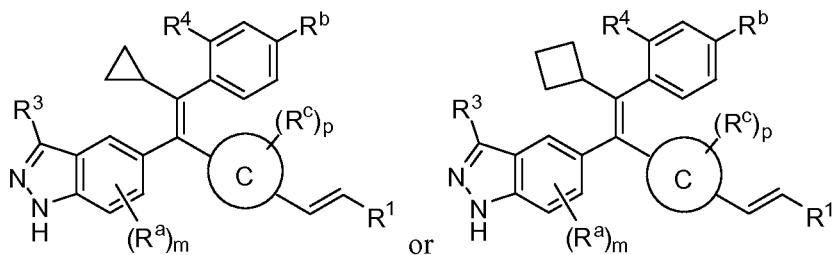
[00186] In some embodiments, the compound of Formula (II) has the following structure:



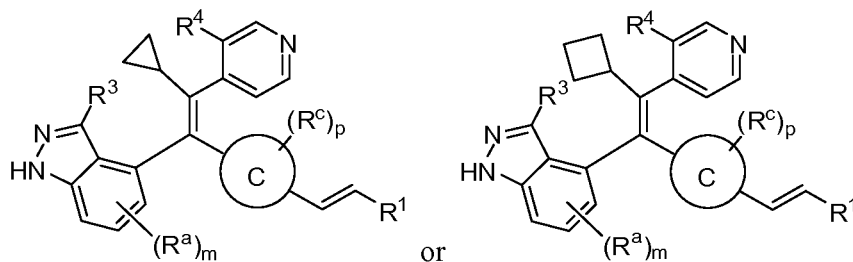
[00187] In some embodiments, the compound of Formula (II) has the following structure:



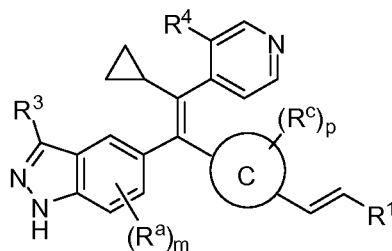
[00188] In some embodiments, the compound of Formula (II) has any one of the following structures:



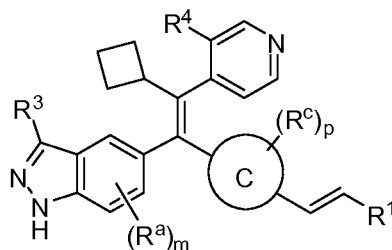
[00189] In some embodiments, the compound of Formula (II) has any one of the following structures:



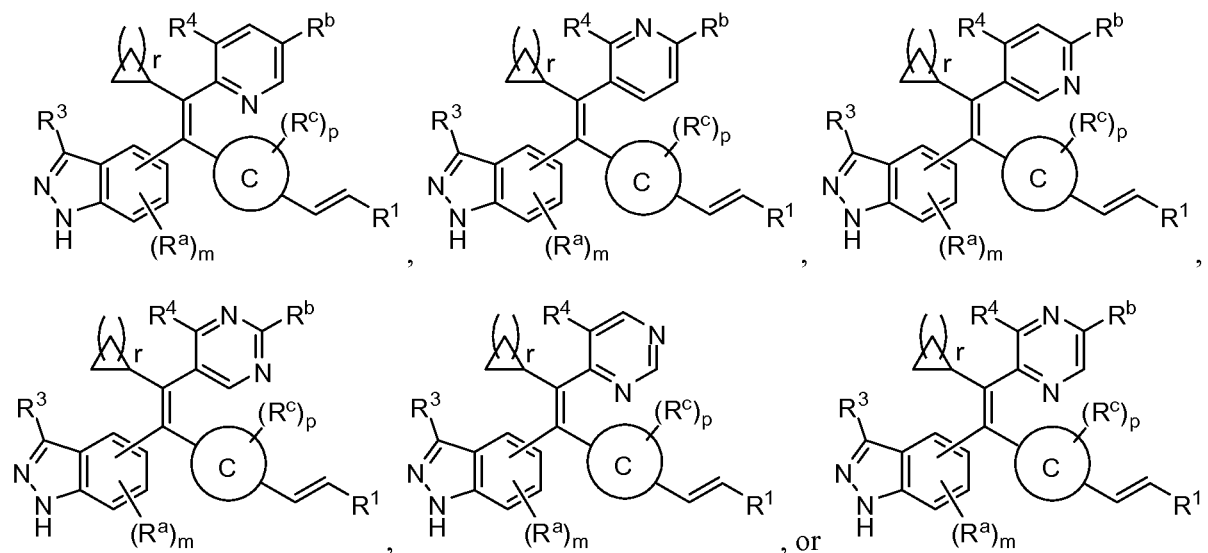
[00190] In some embodiments, the compound of Formula (II) has the following structure:



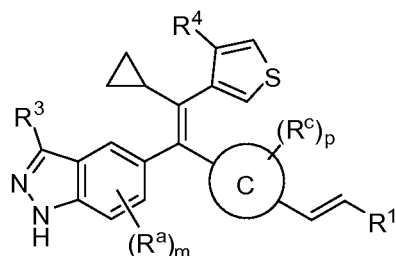
[00191] In some embodiments, the compound of Formula (II) has the following structure:



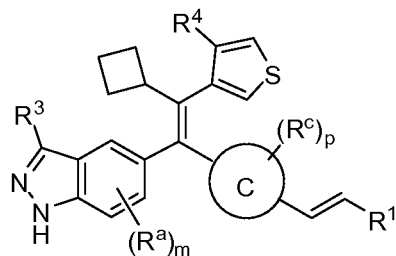
[00192] In some embodiments, the compound of Formula (II) has any one of the following structures:



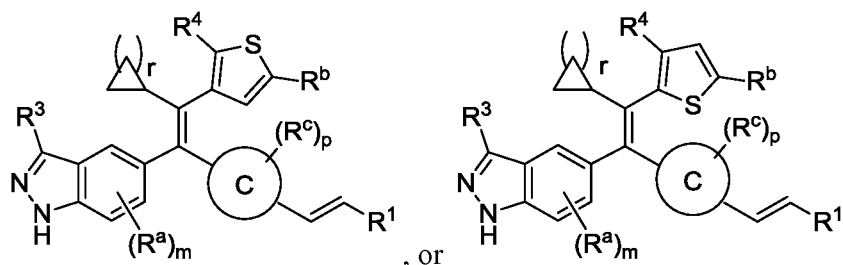
[00193] In some embodiments, the compound of Formula (II) has the following structure:



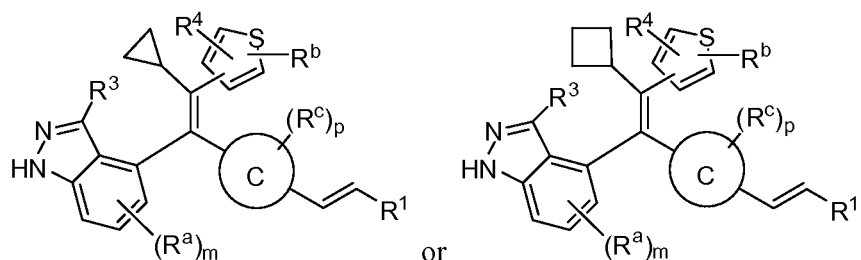
[00194] In some embodiments, the compound of Formula (II) has the following structure:



[00195] In some embodiments, the compound of Formula (II) has any one of the following structures:



[00196] In some embodiments, the compound of Formula (II) has any one of the following structures:



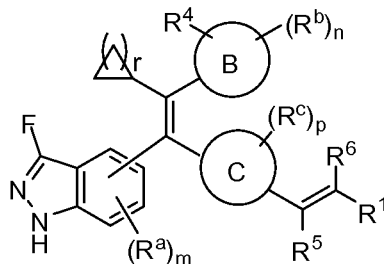
[00197] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R⁴ is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[00198] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R⁴ is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00199] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R⁴ is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00200] In some embodiments, R³ is H, F, Cl, -CN, -CH₃, or -CF₃.

[00201] In another aspect, described herein is compound of Formula (III), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (III)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^5 is H, C_1 - C_4 alkyl, or halogen;

R^6 is H, C_1 - C_4 alkyl, or halogen;

R^7 is H, or C_1 - C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

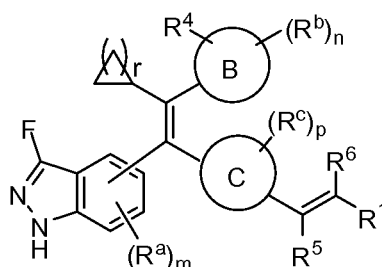
provided that the compound is not

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;
 (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;
 (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide;
 (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide; or
 (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

[00202] In another aspect, described herein is compound of Formula (III), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (III)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, 5-membered monocyclic heterocycle containing at least one N atom or a 6-membered monocyclic heterocycle containing at least one N atom;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-

C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R⁴ is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R⁵ is H, C₁-C₄alkyl, or halogen;

R⁶ is H, C₁-C₄alkyl, or halogen;

R⁷ is H, or C₁-C₆alkyl;

each R⁸ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R⁹ is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

provided that the compound is not

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

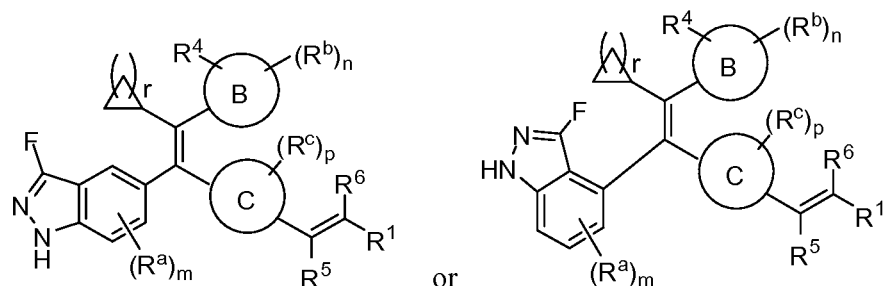
(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide;

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

or

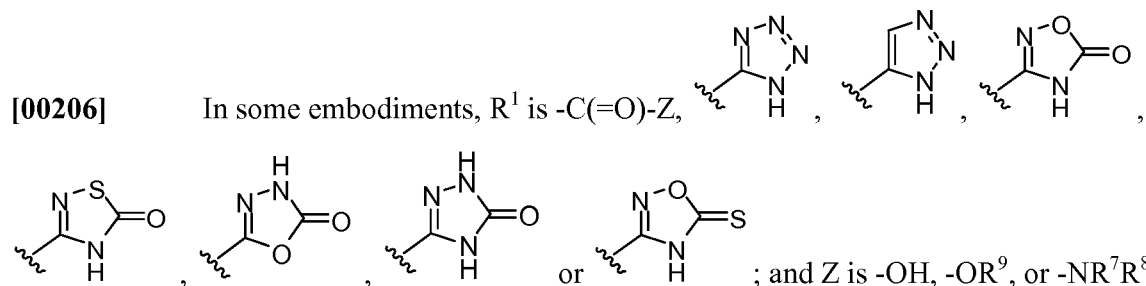
(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

[00203] In some embodiments, the compound of Formula (III) has any one of the following structures:

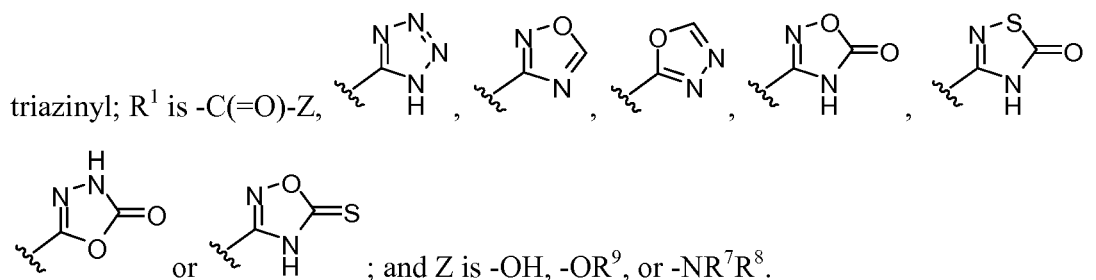


[00204] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

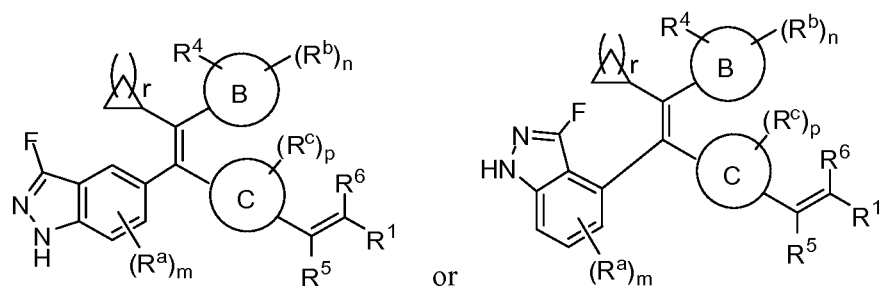
[00205] In some embodiments, ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl.



[00207] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



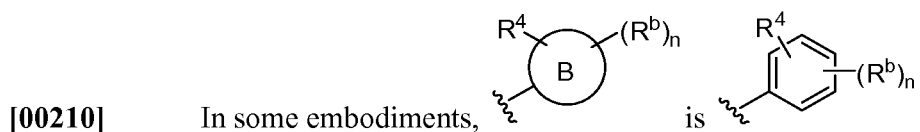
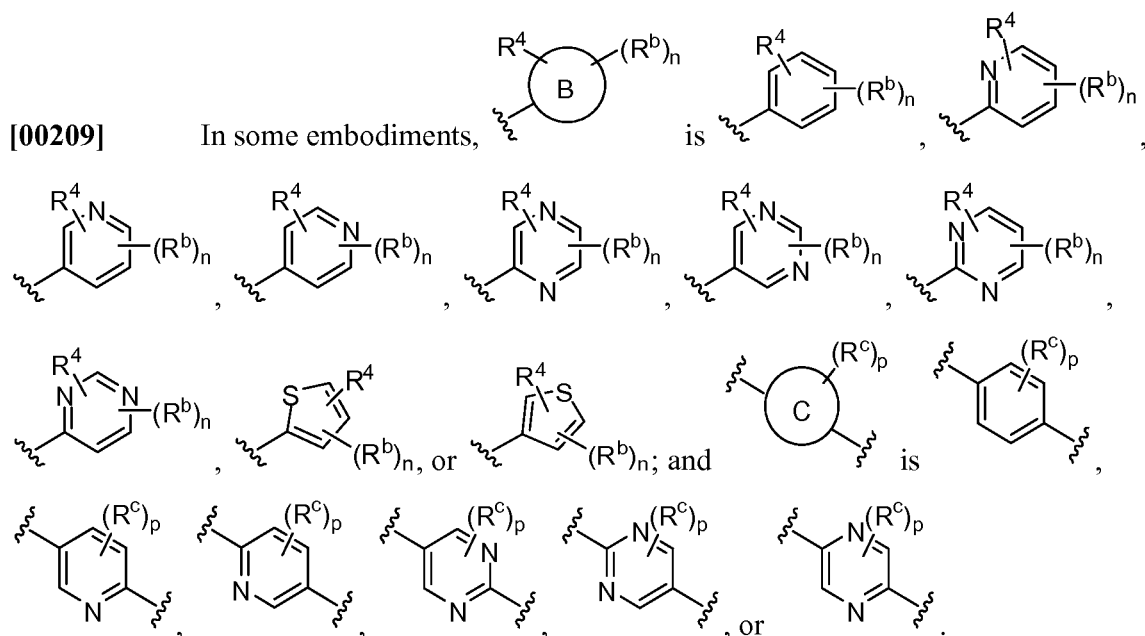
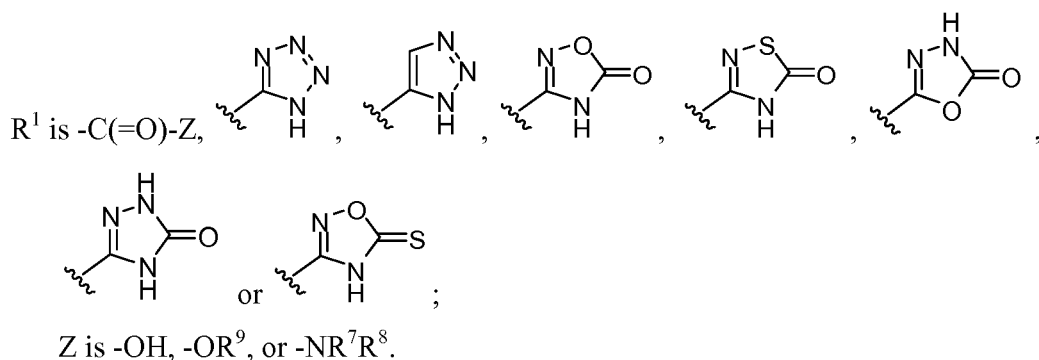
[00208] In some embodiments, the compound of Formula (III) has any one of the following structures:



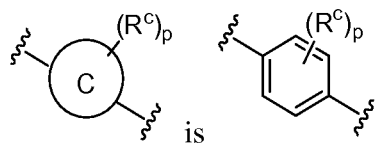
wherein:

ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl;

ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl;



[00211] In some embodiments,

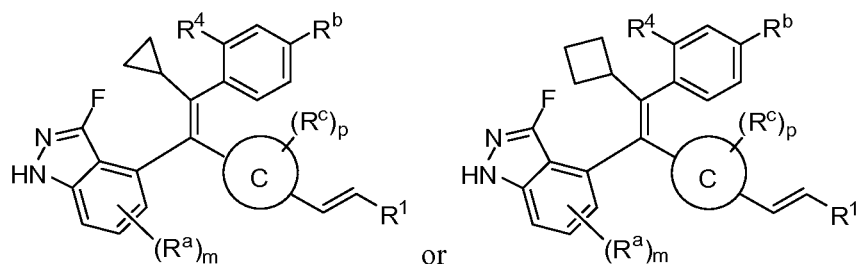


is

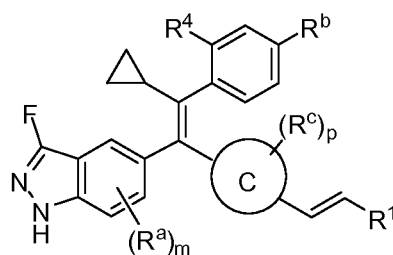
[00212] In some embodiments, r is 1.

[00213] In some embodiments, r is 2.

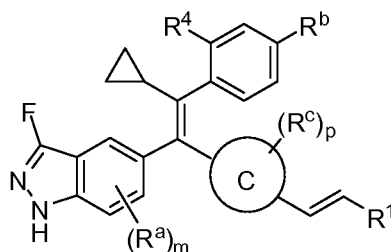
[00214] In some embodiments, the compound of Formula (III) has any one of the following structures:



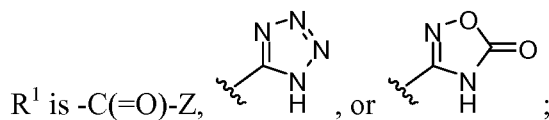
[00215] In some embodiments, the compound of Formula (III) has the following structure:



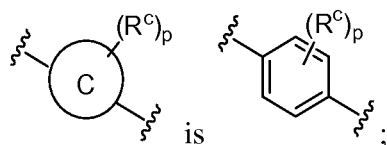
[00216] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is $-OH$;



is

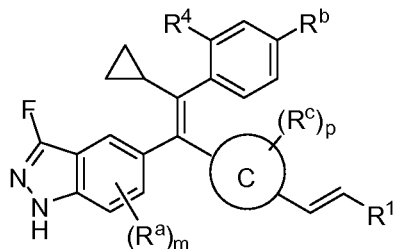
R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

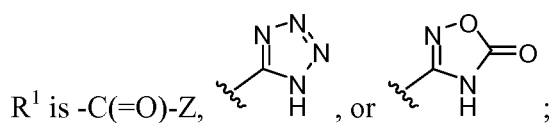
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;
 m is 0 or 1;
 p is 0 or 1.

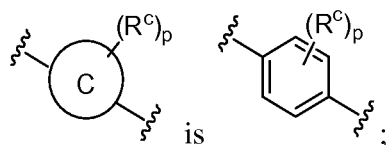
[00217] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is -OH;



R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^b is Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

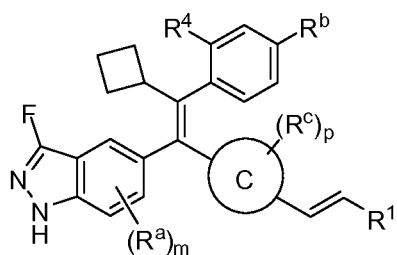
R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃;

R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

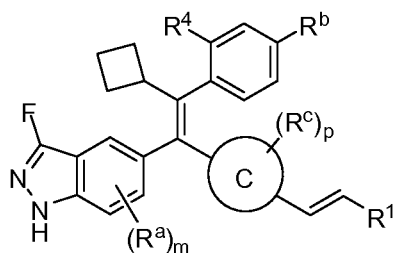
m is 0 or 1;

p is 0 or 1.

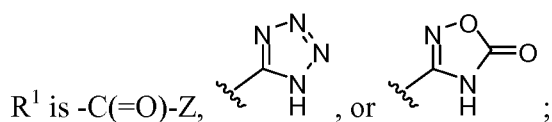
[00218] In some embodiments, the compound of Formula (III) has the following structure:



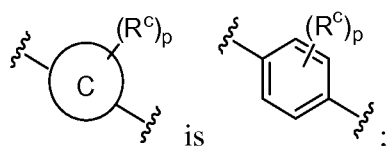
[00219] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is $-OH$;



R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

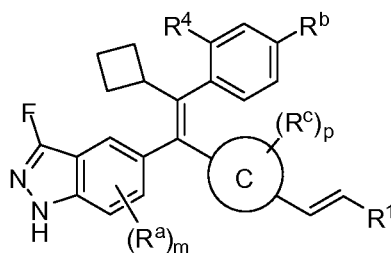
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

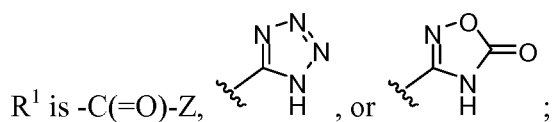
m is 0 or 1;

p is 0 or 1.

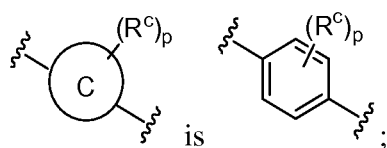
[00220] In some embodiments, the compound of Formula (III) has the following structure:



wherein,



Z is $-OH$;



R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is Cl, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

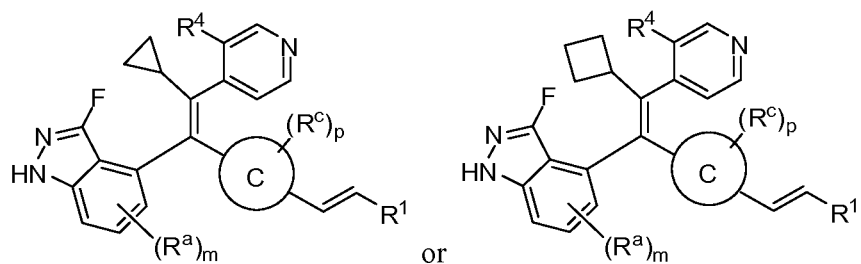
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

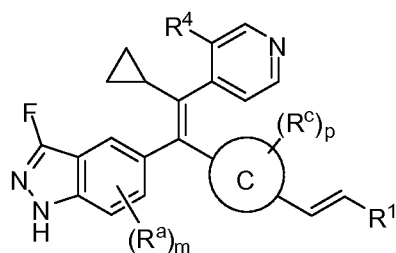
m is 0 or 1;

p is 0 or 1.

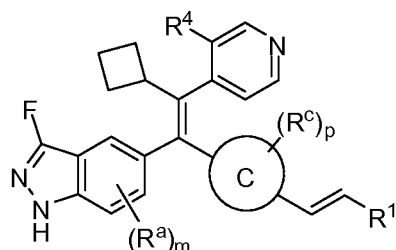
[00221] In some embodiments, the compound of Formula (III) has any one of the following structures:



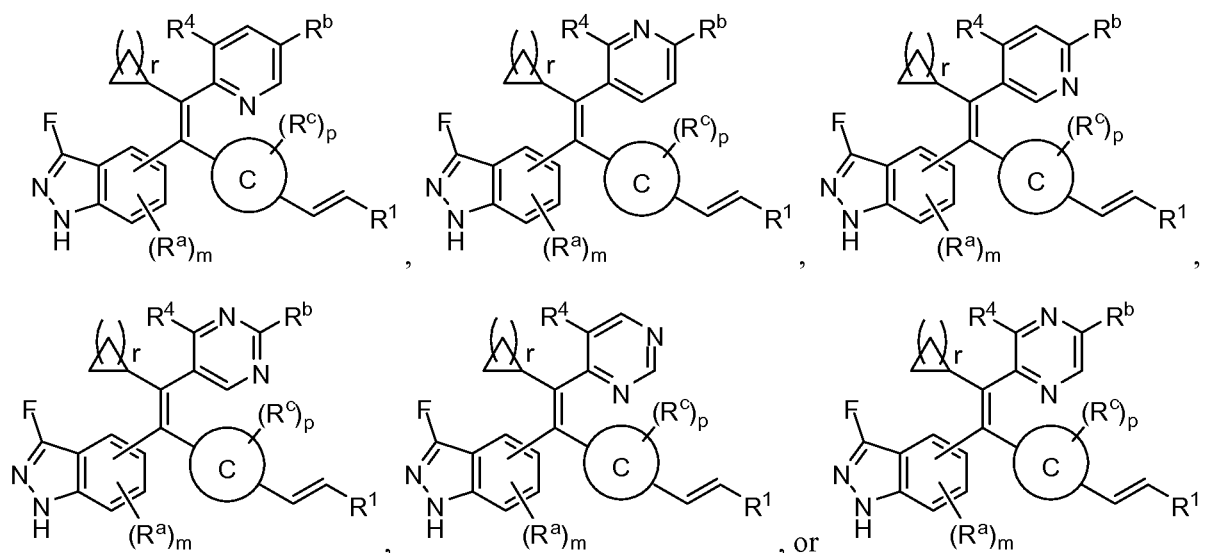
[00222] In some embodiments, the compound of Formula (III) has the following structure:



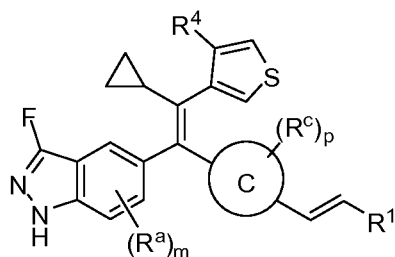
[00223] In some embodiments, the compound of Formula (III) has the following structure:



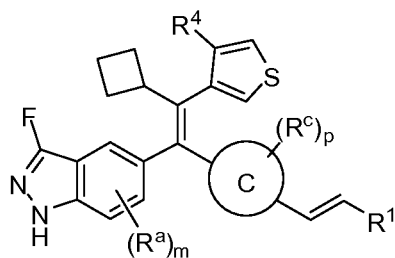
[00224] In some embodiments, the compound of Formula (III) has any one of the following structures:



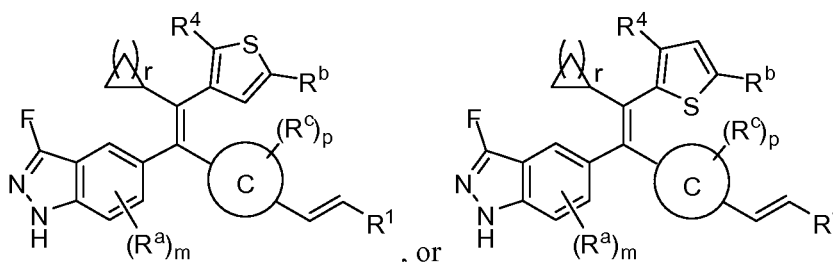
[00225] In some embodiments, the compound of Formula (III) has the following structure:



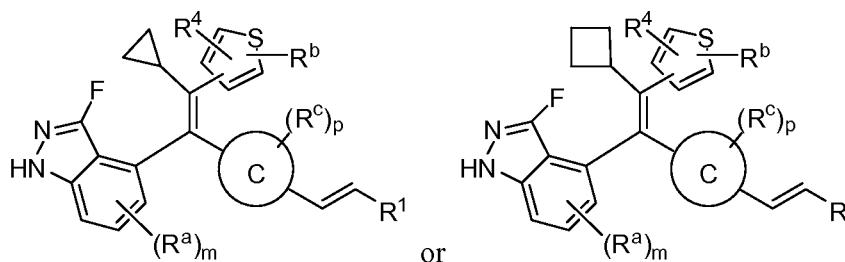
[00226] In some embodiments, the compound of Formula (III) has the following structure:



[00227] In some embodiments, the compound of Formula (III) has any one of the following structures:



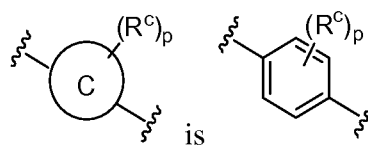
[00228] In some embodiments, the compound of Formula (III) has any one of the following structures:



[00229] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[00230] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

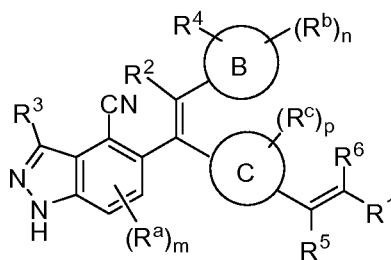
[00231] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; and R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.



[00232] In some embodiments, is ; R^a is H, F, Cl, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl; R^b is H, F, Cl, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl; R^c is H, F, Cl, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl; R^4 is H, F, Cl, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl; m is 0 or 1; p is 0 or 1.

[00233] In some embodiments, R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_2CH_3$, $-OCH_3$, $-CH_3$, or $-CF_3$; R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$.

[00234] In yet another aspect, described herein is a compound of Formula (IV), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (IV)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

R^2 is C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, C_1 - C_6 deuteroalkyl, or C_3 - C_6 cycloalkyl;

R^3 is H, halogen, $-CN$, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, and substituted or unsubstituted C_1 - C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, -

$\text{NR}^7\text{C}(=\text{O})\text{OR}^9$, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkynyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkoxy, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ fluoroalkyl;

R^4 is H, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, $-\text{SR}^8$, $-\text{S}(=\text{O})\text{R}^9$, $-\text{S}(=\text{O})_2\text{R}^9$, $-\text{NHS}(=\text{O})_2\text{R}^9$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^9$, $-\text{OC}(=\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^8)_2$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ fluoroalkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl;

R^5 is H, $\text{C}_1\text{-C}_4$ alkyl, or halogen;

R^6 is H, $\text{C}_1\text{-C}_4$ alkyl, or halogen;

R^7 is H, or $\text{C}_1\text{-C}_6$ alkyl;

each R^8 is independently selected from H, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkynyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

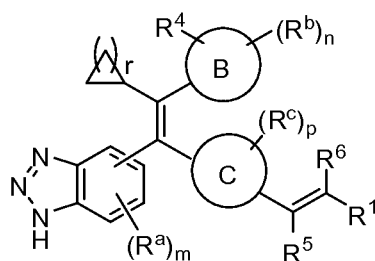
each R^9 is independently selected from substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, or 2;

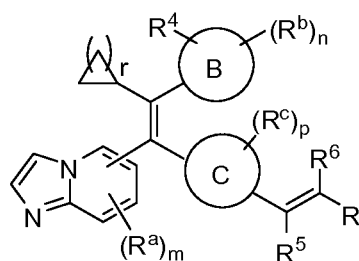
n is 0, 1, 2, or 3; and

p is 0, 1, or 2.

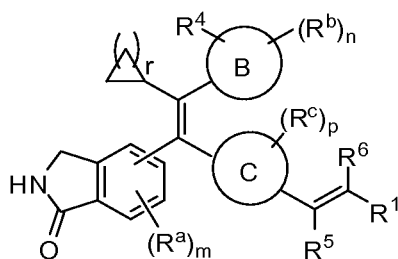
[00235] In an further aspect, described herein is a compound of Formula (V), Formula (VI), Formula (VII), Formula (VIII) or Formula (IX) or a pharmaceutically acceptable salt, or N-oxide thereof:



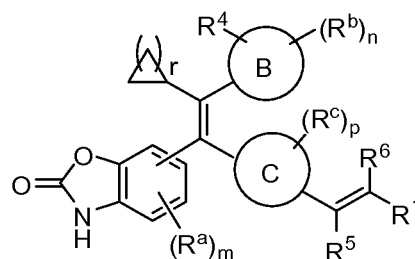
Formula (V)



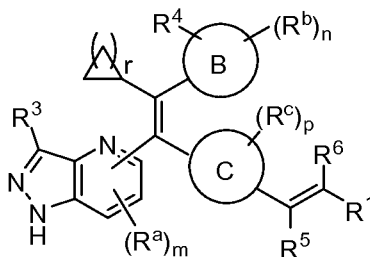
Formula (VI)



Formula (VII)



Formula (VIII)



Formula (IX)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -NR⁷C(=O)OR⁹, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R³ is H, halogen, -CN, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^4 is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^5 is H, C₁-C₄alkyl, or halogen;

R^6 is H, C₁-C₄alkyl, or halogen;

R^7 is H, or C₁-C₆alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

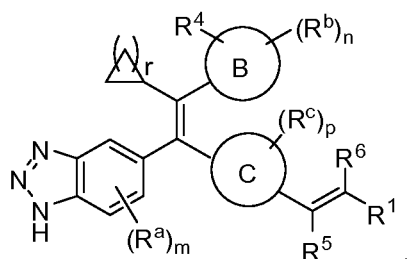
n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

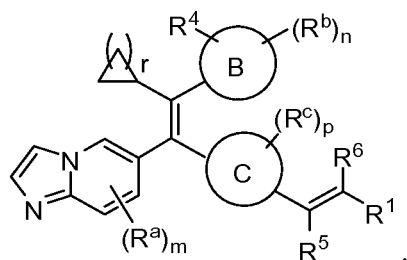
r is 1, 2, 3, or 4;

provided that the compound is not (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid.

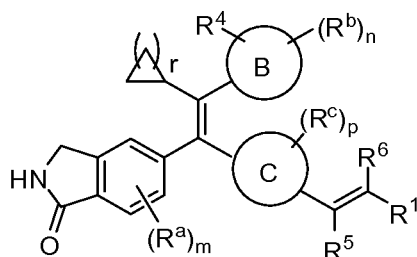
[00236] In some embodiments, the compound of Formula (V) has the following structure:



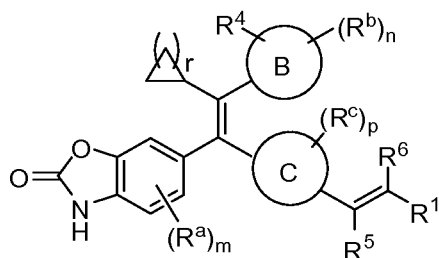
[00237] In some embodiments, the compound of Formula (VI) has the following structure:



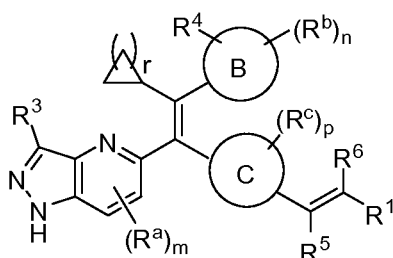
[00238] In some embodiments, the compound of Formula (VII) has the following structure:



[00239] In some embodiments, the compound of Formula (VIII) has the following structure:

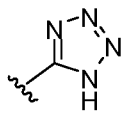
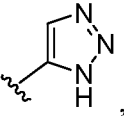
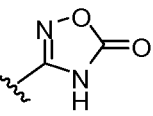


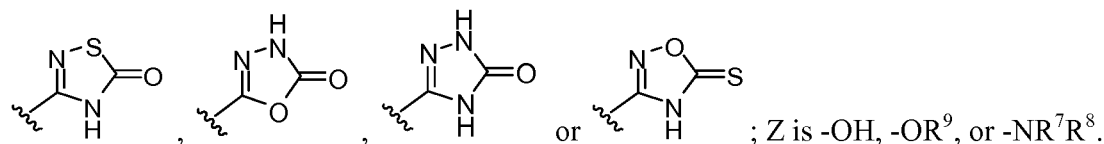
[00240] In some embodiments, the compound of Formula (IX) has the following structure:



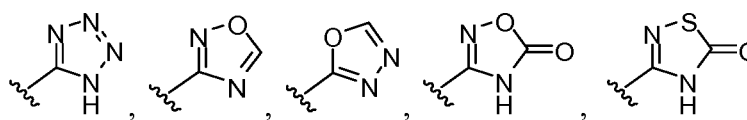
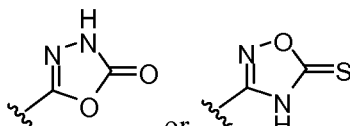
[00241] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl. In some embodiments, ring B is phenyl.

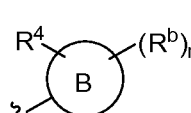
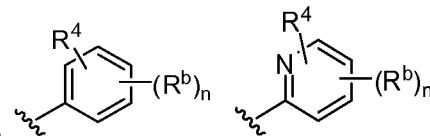
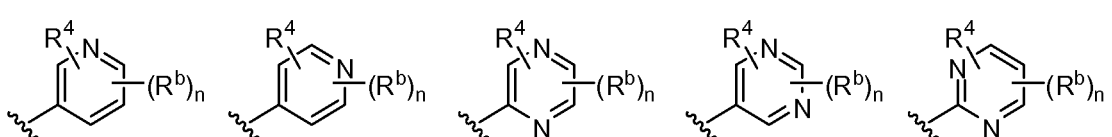
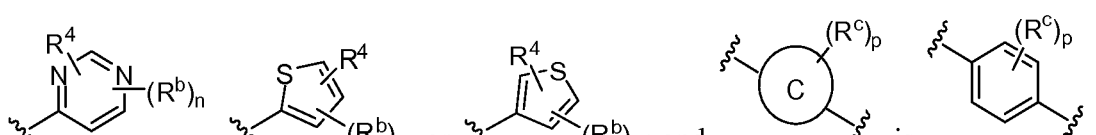
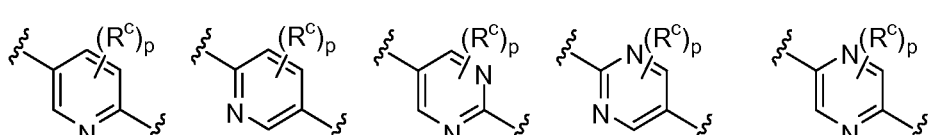
[00242] In some embodiments, ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl. In some embodiments, ring C is phenyl.

[00243] In some embodiments, R¹ is -C(=O)-Z, , , ,



[00244] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or

triazinyl; R^1 is $-C(=O)-Z$, , ; Z is $-OH$, $-OR^9$, or $-NR^7R^8$.

[00245] In some embodiments,  is , , , and .

[00246] In some embodiments, R^b is H, F, Cl, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or C_1-C_6 heteroalkyl; and R^4 is H, F, Cl, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or C_1-C_6 heteroalkyl.

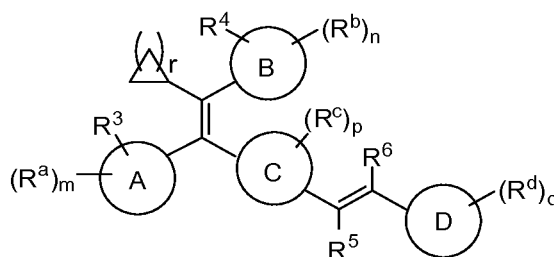
[00247] In some embodiments, R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^5 is H; and R^6 is H.

[00248] In some embodiments, R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$; R^5 is H; and R^6 is H.

[00249] In some embodiments, r is 1.

[00250] In some embodiments, r is 2.

[00251] In another aspect, described herein is a compound of Formula (X), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (X)

wherein,

ring A is 8-, 9- or 10-membered bicyclic heteroaryl;

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or 6-membered monocyclic heteroaryl;

ring D is a 5-membered heterocycle or a 6-membered heterocycle;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$,

substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, and substituted or unsubstituted C_1 - C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, -

$S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, -

OCO_2R^9 , $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, -

$NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 -

C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 -

C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted

C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted

phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 -

C_6 fluoroalkyl;

each R^d is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, -

$S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, -

OCO_2R^9 , $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, -

$NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 -

C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 -

C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted

C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted

phenyl and substituted or unsubstituted monocyclic heteroaryl;

R^3 is H, halogen, $-CN$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 -

C_6 heteroalkyl;

R^4 is H, halogen, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^5 is H, C₁-C₄alkyl, or halogen;

R^6 is H, C₁-C₄alkyl, or halogen;

R^7 is H, or C₁-C₆alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2;

q is 0, 1, 2, or 3; and

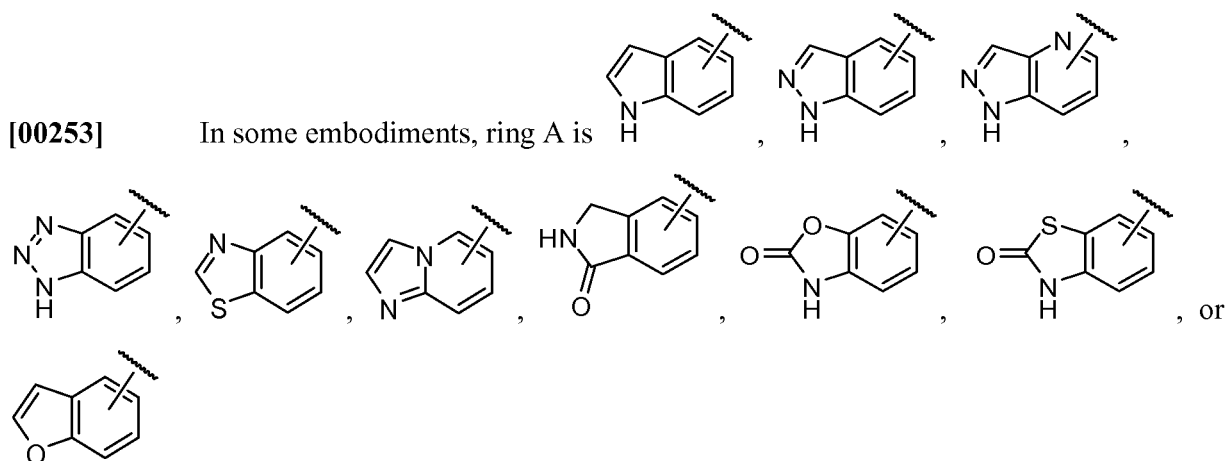
r is 1, 2, 3, or 4;

provided that the compound is not 5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)benzo[d]thiazole.

[00252] In some embodiments, ring A is quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, indazolyl, azaindazolyl, benzimidazolyl, azabenzimidazolyl, benzotriazolyl, azabenzotriazolyl, benzoxazolyl, azabenzoxazolyl, benzisoxazolyl, azabenzisoxazolyl, benzofuranyl, azabenzofuranyl, benzothienyl, azabenzothienyl, benzothiazolyl, azabenzothiazolyl, or purinyl.

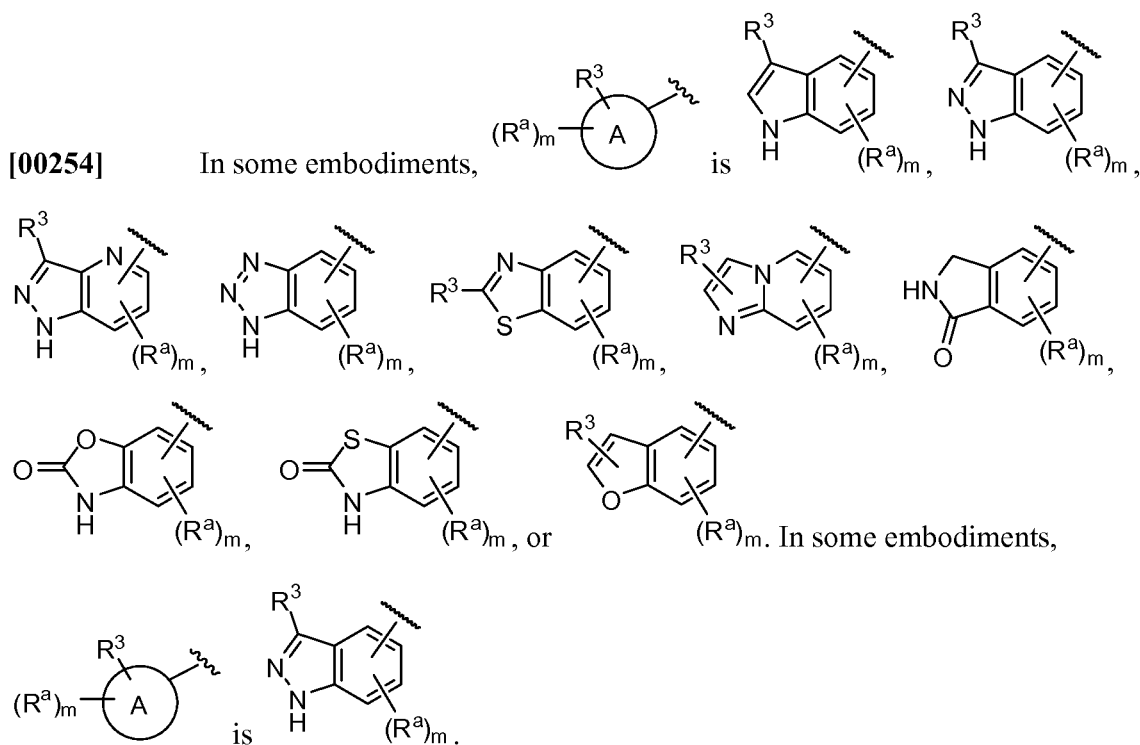
[00253]

In some embodiments, ring A is



[00254]

In some embodiments,



[00255]

In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl. In some embodiments, ring B is phenyl. In some embodiments, ring B is furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, or thiadiazolyl. In some embodiments, ring B is thienyl. In some embodiments, ring B is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00256]

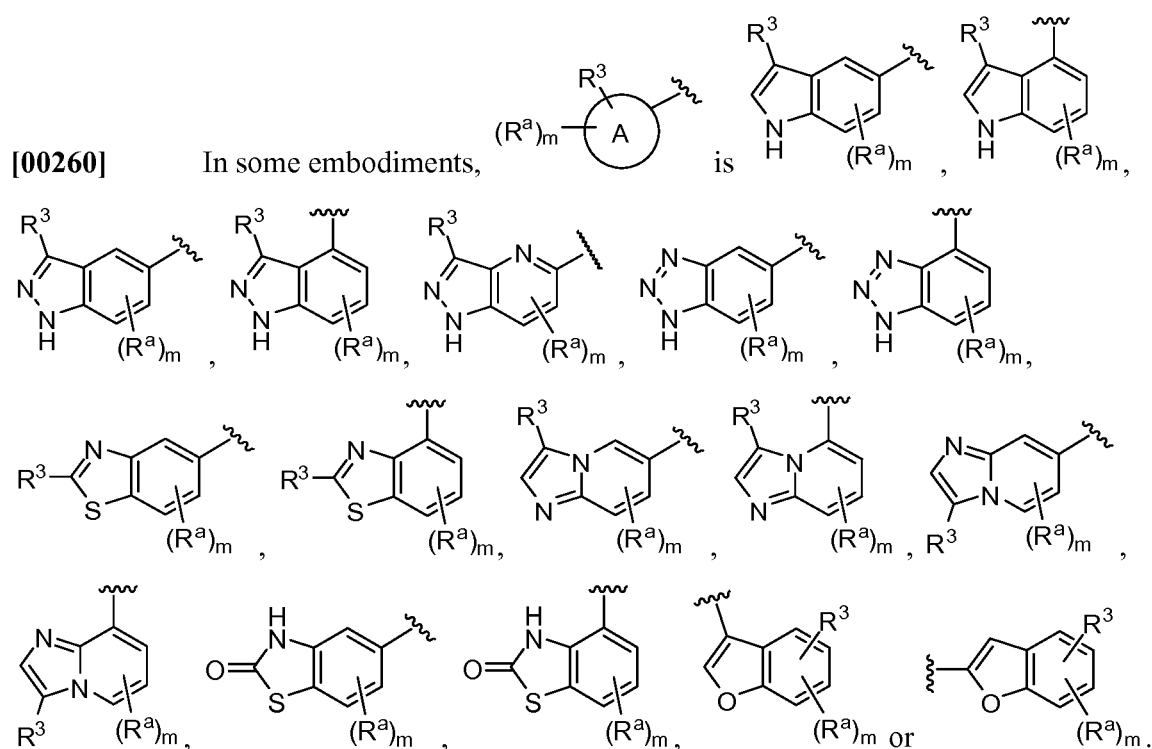
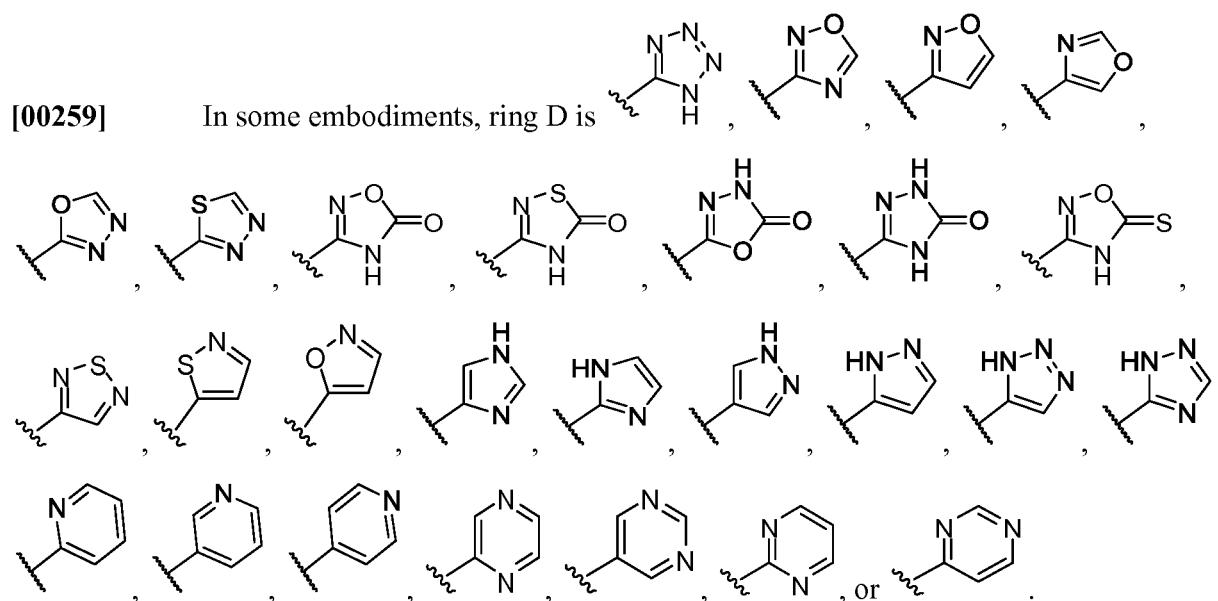
In some embodiments, ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl. In some embodiments, ring C is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl. In some embodiments, ring C is phenyl.

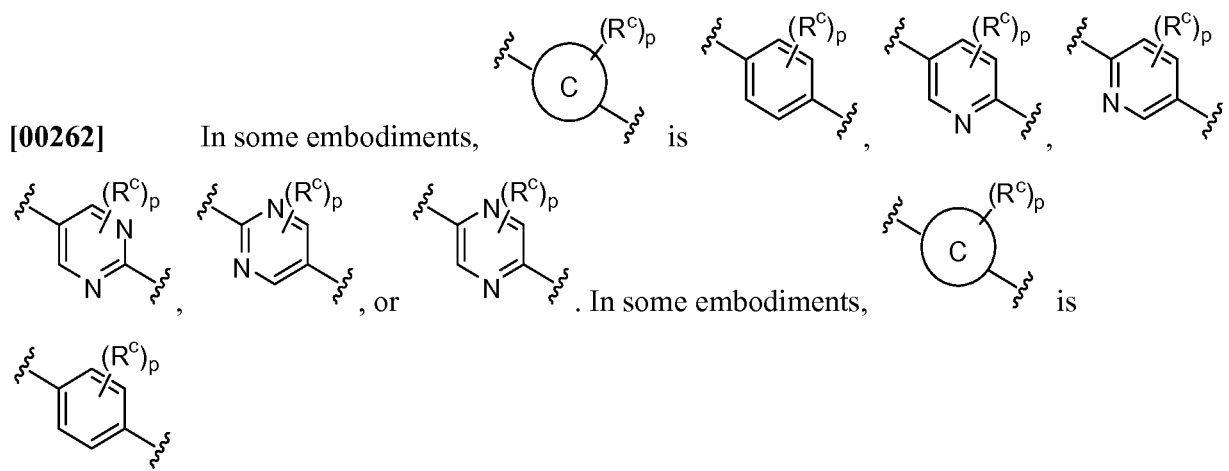
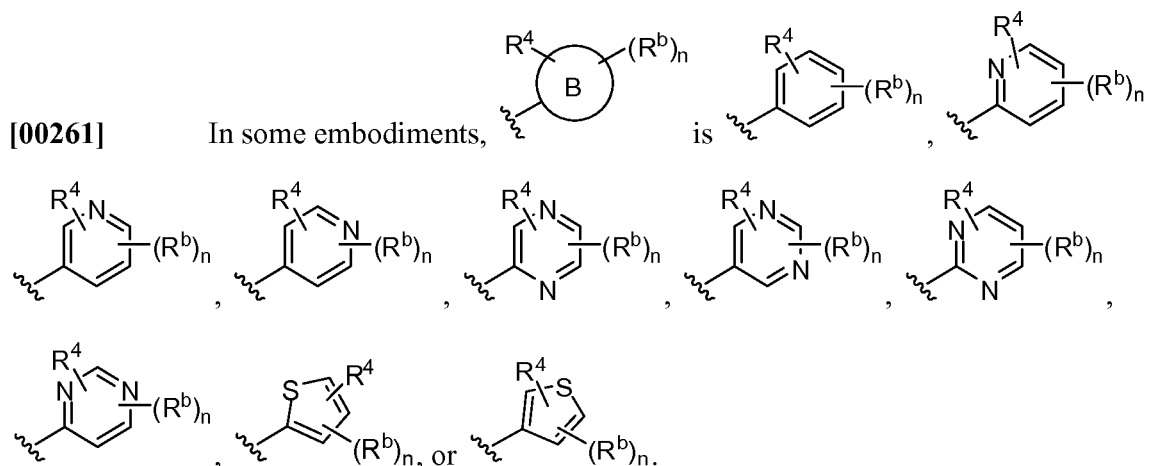
[00257]

In some embodiments, ring D is a 5-membered heterocycle or a 6-membered heterocycle comprising 1-4 N atoms in the ring. In some embodiments, ring D is a 5-membered

heterocycle comprising 1-4 N atoms in the ring. In some embodiments, ring D is a 6-membered heterocycle comprising 1-3 N atoms in the ring. In some embodiments, ring D is a 6-membered heteroaryl comprising 1-3 N atoms in the ring.

[00258] In some embodiments, ring D is furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl. In some embodiments, ring D is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl. In some embodiments, ring D is pyridinyl. In some embodiments, ring D is furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, or thiadiazolyl.





[00263] In some embodiments, R^5 is H; and R^6 is H.

[00264] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[00265] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

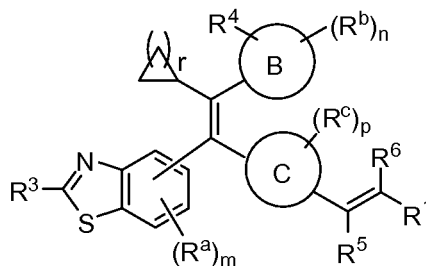
[00266] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH; R^5 is H; and R^6 is H.

[00267] In some embodiments, R^d is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl. In some embodiments, R^d is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00268] In some embodiments, r is 1 or 2. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4.

[00269] In some embodiments, q is 0, 1, 2, or 3. In some embodiments, q is 0, 1, or 2. In some embodiments, q is 0, or 1.

[00270] In yet a further aspect, described herein is a compound of Formula (XI), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (XI)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

R^3 is H, halogen, $-CN$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, and substituted or unsubstituted C_1 - C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkoxy, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1 - C_6 alkyl, or C_1 - C_6 fluoroalkyl;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 fluoroalkyl, or C_1 - C_6 heteroalkyl;

R^5 is H, C_1 - C_4 alkyl, or halogen;

R^6 is H, C_1 - C_4 alkyl, or halogen;

R^7 is H, or C_1 - C_6 alkyl;

each R^8 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl,

substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl,

substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted or unsubstituted C_1 -

C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted

C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted

monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or

unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_1 - C_6 fluoroalkyl, substituted

or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted

or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

provided that the compound is not (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-

fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-

2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-

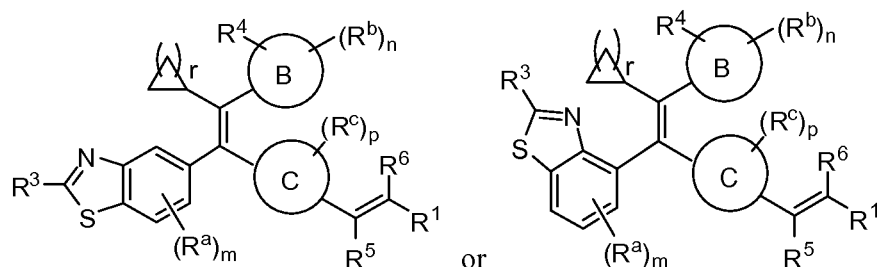
(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-4-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-

((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid; or 5-((E)-1-

(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(4-methylthiophen-3-

yl)vinyl)benzo[d]thiazole.

[00271] In some embodiments, the compound of Formula (XI) has any one of the following structures:

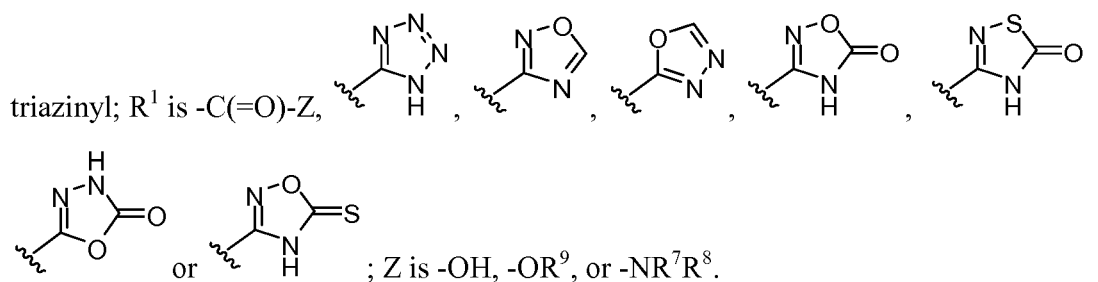


[00272] In some embodiments, r is 1.

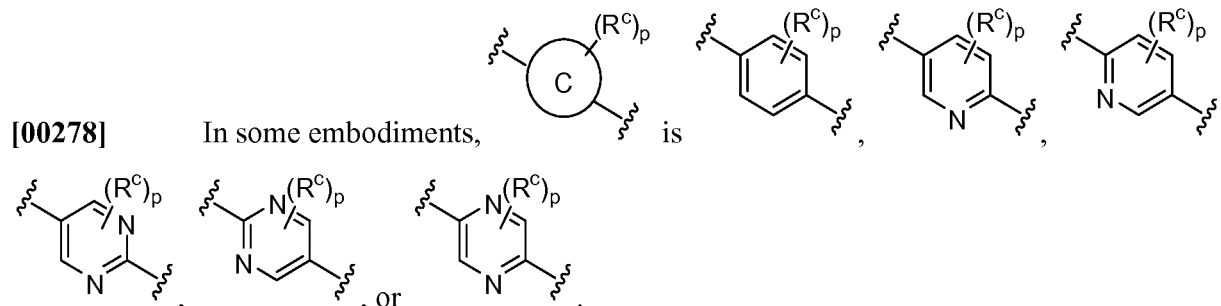
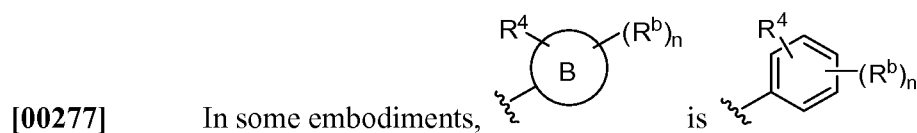
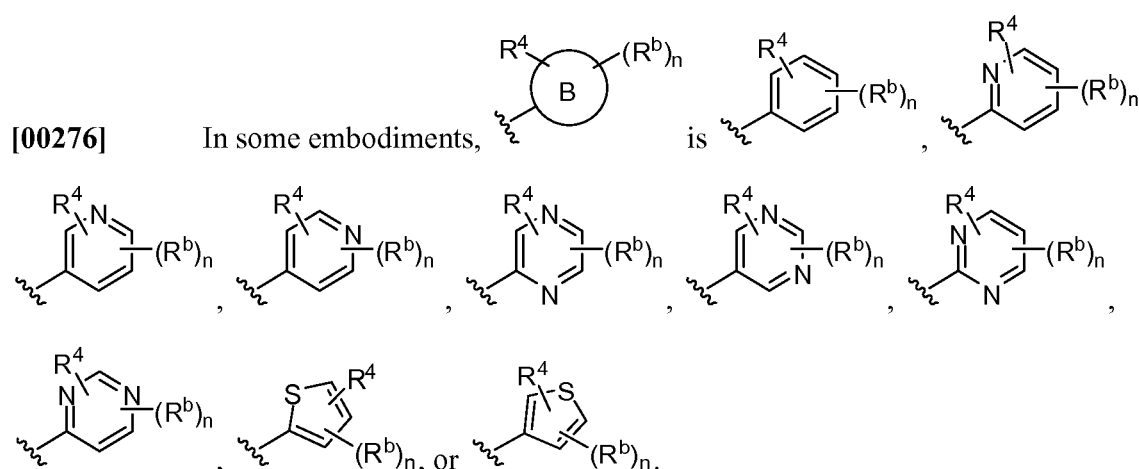
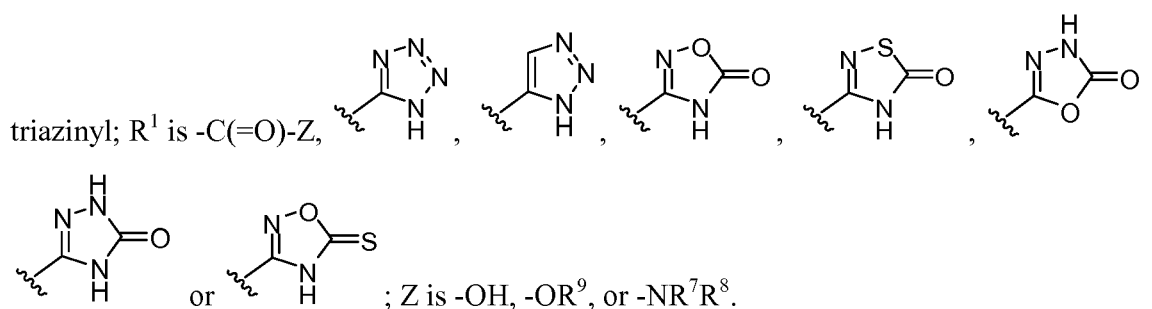
[00273] In some embodiments, r is 2.

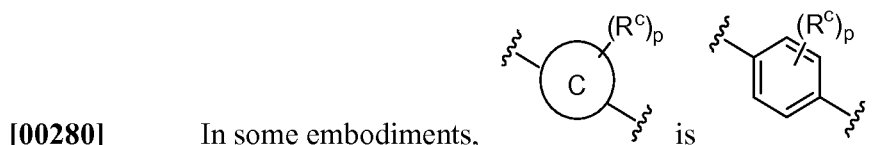
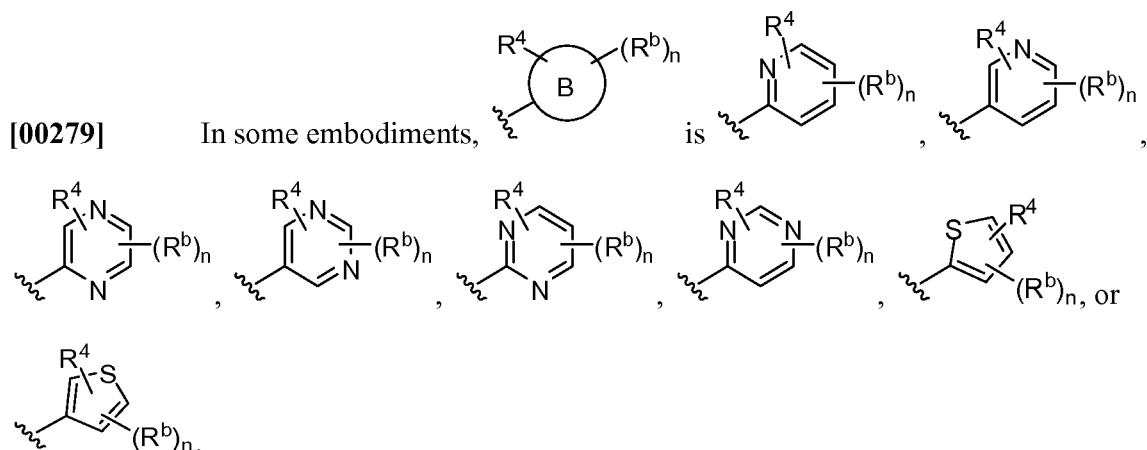
[00274] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl,

thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or



[00275] In some embodiments, ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or





[00281] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl; and R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.

[00282] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00283] In some embodiments, R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00284] In some embodiments, R^b is not H. In some embodiments, R^b is not F. In some embodiments, R^b is not H or F.

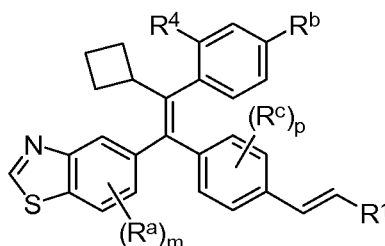
[00285] In some embodiments, R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

[00286] In some embodiments, R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

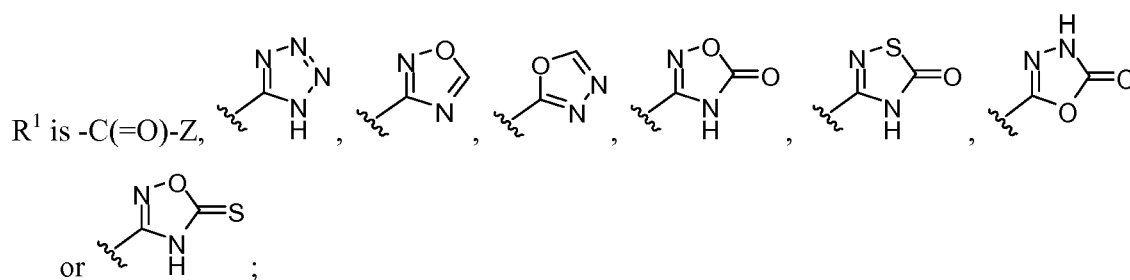
[00287] In some embodiments, R^4 is not H.

[00288] In some embodiments, R^5 is H. In some embodiments, R^6 is H. In some embodiments, R^5 is H; and R^6 is H.

[00289] In some embodiments, the compound of Formula (XI) has the following structure, or a pharmaceutically acceptable salt, or N-oxide thereof:



wherein,



Z is $-\text{OH}$;

R^a is H, F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_3$, $-\text{CF}_3$, or $-\text{CH}_2\text{OH}$;

R^b is Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{CH}_3$, $-\text{CF}_3$, or $-\text{CH}_2\text{OH}$;

R^c is H, F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_3$, or $-\text{CF}_3$;

R^d is H, F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{CH}_3$, $-\text{CF}_3$, or $-\text{CH}_2\text{OH}$;

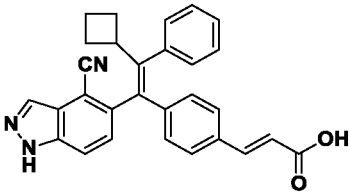
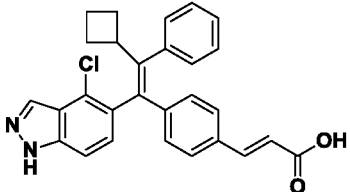
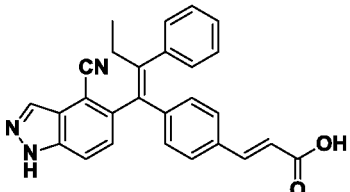
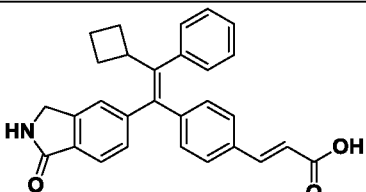
m is 0 or 1;

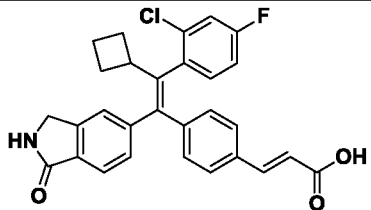
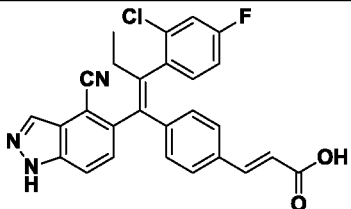
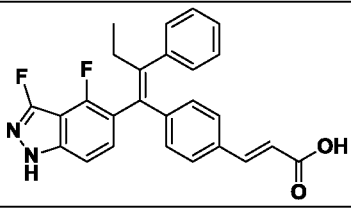
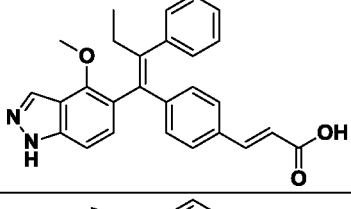
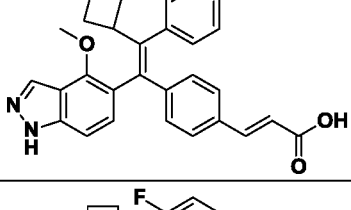
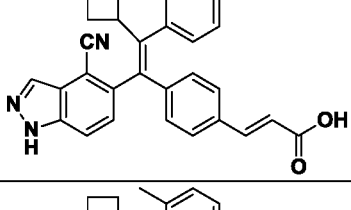
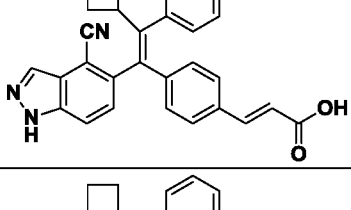
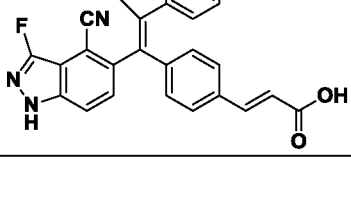
p is 0 or 1.

[00290] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00291] In some embodiments, described herein is a compound in Table 1, or a pharmaceutically acceptable salt thereof:

Table 1.

Example	Name	Structure
1	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	
2	(E)-3-(4-((E)-1-(4-Chloro-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	
3	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
4	(E)-3-(4-((E)-2-Cyclobutyl-1-(1-oxoisindolin-5-yl)-2-phenylvinyl)phenyl)acrylic acid	

Example	Name	Structure
5	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1-oxoisindolin-5-yl)vinyl)phenyl)acrylic acid	
6	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
7	(E)-3-(4-((E)-1-(3,4-Difluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
8	(E)-3-(4-((E)-1-(4-Methoxy-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
9	(E)-3-(4-((E)-2-Cyclobutyl-1-(4-methoxy-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
10	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
11	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid	
12	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	

Example	Name	Structure
13	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-cyclopropyl-2-phenylvinyl)phenyl)acrylic acid	
14	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-phenylvinyl)phenyl)acrylic acid	
15	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-3-methyl-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
16	(E)-3-(4-((E)-2-(4-Chloro-2-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)-3-methylbut-1-en-1-yl)phenyl)acrylic acid	
17	(E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	
18	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-4-yl)-2-phenylvinyl)phenyl)acrylic acid	
19	(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
20	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-3-methyl-2-(4-methylthiophen-3-yl)but-1-en-1-yl)phenyl)acrylic acid	
21	(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	

Example	Name	Structure
22	(E)-3-(4-((E)-2-Cyclobutyl-1-(4,7-difluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
23	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid	
24	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid	
25	(E)-3-(4-((E)-2-Cyclobutyl-1-(4-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
26	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
27	(E)-3-(4-((E)-2-Cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-2-phenylvinyl)phenyl)acrylic acid	
28	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)vinyl)phenyl)acrylic acid	
29	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid	
30	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
31	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid	
32	(E)-3-(4-((E)-1-(4,7-Difluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid	
33	(E)-3-(4-((E)-2-Cyclobutyl-2-phenyl-1-(1H-pyrazolo[4,3-b]pyridin-5-yl)vinyl)phenyl)acrylic acid	
34	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1H-pyrazolo[4,3-b]pyridin-5-yl)vinyl)phenyl)acrylic acid	
35	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(1H-indazol-5-yl)-3-methylbut-1-en-1-yl)phenyl)acrylic acid	
36	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylic acid	
37	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-2-methylphenyl)acrylic acid	
38	(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-methoxyphenyl)acrylic acid	
39	5-((E)-1-(4-((E)-2-(1H-Imidazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	

Example	Name	Structure
40	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
41	(E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-((trifluoromethyl)sulfonyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid	
42	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
43	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
44	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
45	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-((trifluoromethyl)sulfonyl)phenyl)vinyl)phenyl)acrylic acid	
46	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid	
47	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-4-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
48	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
49	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
50	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
51	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluoro-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
52	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-fluoropyridin-4-yl)vinyl)phenyl)acrylic acid	
53	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
54	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
55	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
56	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(3-((6-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid	
57	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(3-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid	
58	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(4-((6-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid	
59	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid	
60	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
61	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
62	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,4-dicyanophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
63	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(4-methoxy-2-methylphenyl)but-1-en-1-yl)phenyl)acrylic acid	

Example	Name	Structure
64	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid	
65	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid	
66	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
67	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
68	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid	
69	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-2-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
70	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(6-methoxy-2-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid	
71	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid	

Example	Name	Structure
72	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylthio)phenyl)vinyl)phenyl)acrylic acid	
73	(E)-3-(4-((E)-2-(2-Chloro-4-(methylthio)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
74	(E)-3-(4-((E)-2-(3-Cyanopyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
75	(E)-3-(4-((E)-1-(Benzofuran-2-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
76	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylic acid	
77	(E)-3-(4-((E)-1-(Benzofuran-2-yl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
78	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylic acid	
79	(E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	

Example	Name	Structure
80	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
81	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxypyridin-4-yl)vinyl)phenyl)acrylic acid	
82	(E)-3-(4-((E)-2-(4-Cyanothiophen-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
83	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid	
84	(E)-3-(4-((E)-2-(3-(1H-Pyrazol-1-yl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
85	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
86	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid	
87	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(pyrrolidin-1-yl)phenyl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
88	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyanothiophen-3-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
89	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxy-3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid	
90	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
91	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid	
92	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid	
93	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid	
94	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
95	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	

Example	Name	Structure
96	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-methylphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
97	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
98	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid	
99	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid	
100	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
101	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
102	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
103	((E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	

Example	Name	Structure
104	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
105	((E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
106	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
107	((E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
108	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
109	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
110	(E)-3-(4-((E)-2-Cyclobutyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
111	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxy-(trifluoromethyl)pyrimidin-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
112	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
113	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid	
114	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
115	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid	
116	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
117	(E)-3-(4-((E)-2-Cyclopropyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
118	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
119	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
120	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
121	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
122	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)vinyl)phenyl)acrylic acid	
123	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
124	(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
125	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid	
126	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-4-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid	
127	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
128	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(pyridin-3-yl)vinyl)phenyl)acrylic acid	
129	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
130	(E)-3-(4-((E)-2-(5-Chloropyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
131	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-fluoropyridin-3-yl)vinyl)phenyl)acrylic acid	
132	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid	
133	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-6-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
134	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-6-methylpyridin-2-yl)acrylic acid	
135	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-methylpyridin-2-yl)acrylic acid	

Example	Name	Structure
136	(E)-3-(4-((E)-2-(5-Chloro-6-methoxypyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
137	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-fluoro-6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid	
138	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid	
139	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid	
140	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)-6-methylpyridin-2-yl)acrylic acid	
141	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(pyridin-2-yl)vinyl)phenyl)acrylic acid	
142	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid	
143	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
144	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid	
145	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid	
146	(E)-3-(4-((E)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
147	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxypyridin-2-yl)vinyl)phenyl)acrylic acid	
148	(E)-3-(4-((E)-1-(3-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	
149	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid	
150	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,5-dimethylthiophen-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
151	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	

Example	Name	Structure
152	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
153	(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
154	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
155	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
156	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
157	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
158	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methoxy-3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid	
159	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyrazin-2-yl)acrylic acid	

Example	Name	Structure
160	(E)-3-(6-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyridin-3-yl)acrylic acid	
161	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-fluoropyridin-2-yl)acrylic acid	
162	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyrimidin-2-yl)acrylic acid	
163	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1H-indazol-4-yl)but-1-en-1-yl)phenyl)acrylic acid	
164	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-6-methoxypyridin-2-yl)acrylic acid	
165	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-methoxypyridin-2-yl)acrylic acid	
166	(E)-3-(3-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
167	(E)-3-(2-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
168	(E)-3-(5-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	

Example	Name	Structure
169	(E)-3-(5-((Z)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	
170	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)-3-fluoro-1H-indazole	
171	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)but-1-en-1-yl)-3-fluoro-1H-indazole	
172	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)-3-fluoro-1H-indazole	
173	4-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)-1H-indazole	
174	5-((E)-1-(4-((E)-2-(1H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	
175	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)benzo[d]thiazole	
176	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)benzo[d]thiazole	

Example	Name	Structure
177	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)benzo[d]thiazole	
178	6-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)imidazo[1,2-a]pyridine	
179	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)-N-(2-hydroxyethyl)acrylamide	
180	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide	
181	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide	
182	(E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide	
183	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-4-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide	
184	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)phenyl)-N-methylacrylamid	

Example	Name	Structure
185	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)-N-(thiazol-2-yl)acrylamide	
186	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)-N-(thiazol-2-yl)acrylamide	
187	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide	
188	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,3-dihydroxypropyl)acrylamide	
189	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(1,3-dihydroxypropan-2-yl)acrylamide	
190	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide	
191	(E)-N-(2-Chloroethyl)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylamide	
192	(2-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-4,5-dihydrooxazol-5-yl)methanol	

Example	Name	Structure
193	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
194	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
195	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
196	(E)-3-(4-((E)-2-(2-Chloro-4-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
197	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
198	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid	
199	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	

Example	Name	Structure
200	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(2-(2-hydroxyethyl)-2H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
201	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(2-hydroxyethyl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid	
202	3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
203	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylohydrazide	
204	3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
205	5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-3-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole	
206	5-((E)-1-(4-((E)-2-(1H-Pyrazol-4-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	
207	5-((E)-1-(4-((E)-2-(1H-Pyrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	

Example	Name	Structure
208	2-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,3,4-oxadiazole	
209	3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazole	
210	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylimidamide	
211	(E)-3-(4-((E)-2-(4-Carbamoyl-2-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
212	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylic acid	
213	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylic acid	
214	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-hydroxypyridin-4-yl)vinyl)phenyl)acrylic acid	
215	(5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-2-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole	

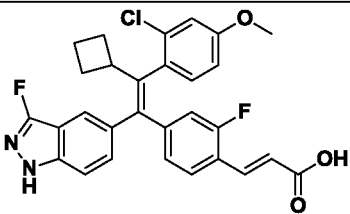
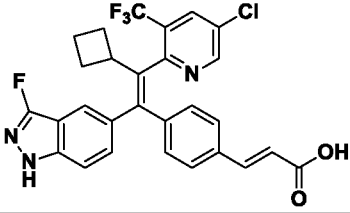
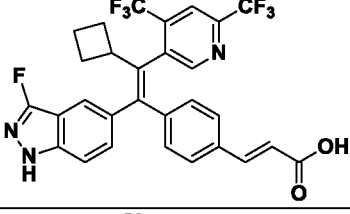
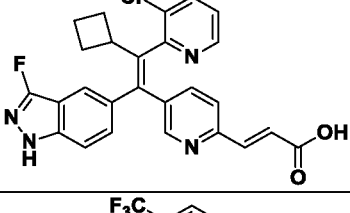
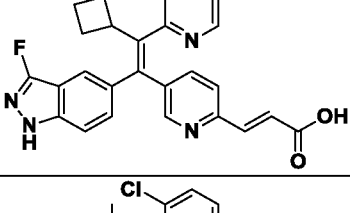
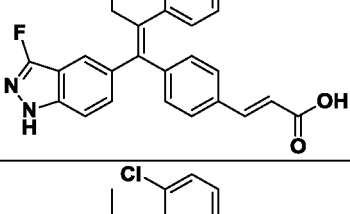
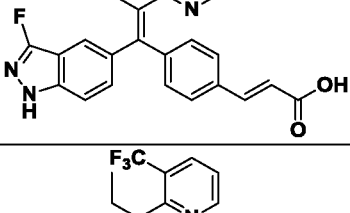
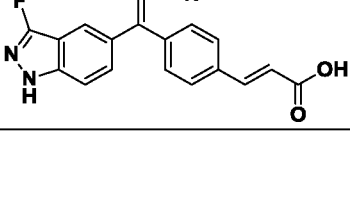
Example	Name	Structure
216	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
217	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid	
218	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
219	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
220	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,4-dichlorophenyl)-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
221	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
222	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	
223	(E)-3-(4-((E)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
224	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(5-cyanoimidazo[1,2-a]pyridin-6-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
225	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
226	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
227	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
228	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
229	(E)-3-(4-((E)-2-Cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid	
230	(E)-3-(4-((E)-2-(2-Chloro-4-ethoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
231	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
232	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
233	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(hydroxymethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
234	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chlorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
235	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-3-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
236	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-5-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
237	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid	
238	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid	
239	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
240	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid	
241	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
242	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
243	(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
244	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
245	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
246	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
247	(E)-3-(4-((E)-2-(3-Cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
248	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
249	(E)-3-(4-((E)-2-(5-Chloro-3-cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
250	(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
251	(E)-3-(4-((E)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
252	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-(trifluoromethyl)-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
253	(E)-3-(4-((Z)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid	
254	(E)-3-(4-((Z)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid	
255	(E)-Ethyl 3-(4-((Z)-2-cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylate	

Example	Name	Structure
256	(E)-3-(4-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid	
257	(E)-3-(4-((E)-2-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
258	(E)-3-(4-((E)-2-(4,6-bis(Trifluoromethyl)pyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
259	(E)-3-(5-((Z)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	
260	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)pyridin-2-yl)acrylic acid	
261	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
262	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
263	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)but-1-en-1-yl)phenyl)acrylic acid	

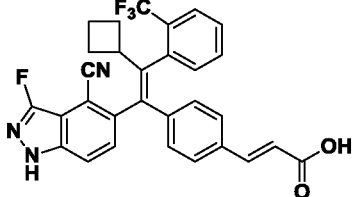
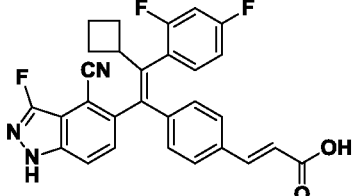
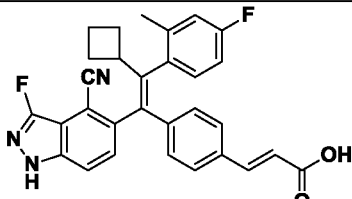
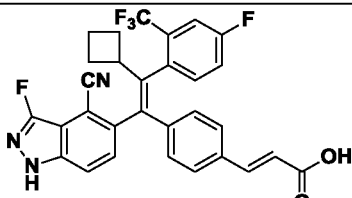
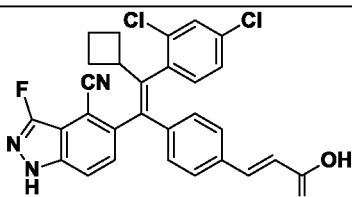
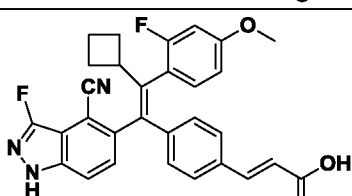
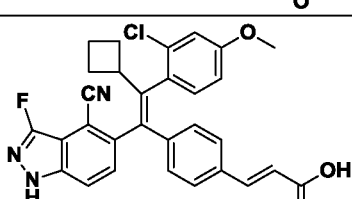
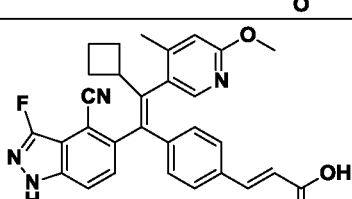
Example	Name	Structure
264	(E)-3-(4-((E)-2-(3,5-Dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid	
265	(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-2-fluorophenyl)acrylic acid	
266	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)but-2-enoic acid	
267	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-2-methylacrylic acid	
268	(E)-3-(5-((Z)-2-Cyclobutyl-2-(2,4-dichlorophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	
269	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)pyridin-2-yl)acrylic acid	
270	(E)-3-(5-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	
271	(E)-3-(4-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid	
272	(E)-3-(5-((Z)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	

Example	Name	Structure
273	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
274	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
275	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
276	3-((E)-4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
277	3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
278	3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
279	3-((E)-4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one	
280	2-((E)-1-Cyclobutyl-2-(3-fluoro-1H-indazol-5-yl)-2-(4-((E)-2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)vinyl)phenyl)vinyl)-5-(trifluoromethyl)benzonitrile	

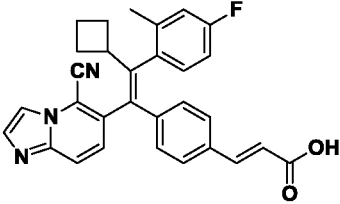
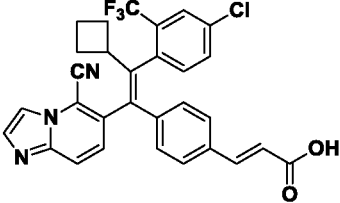
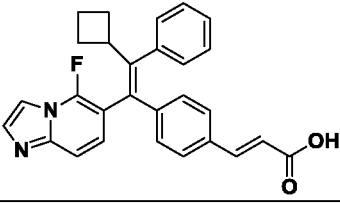
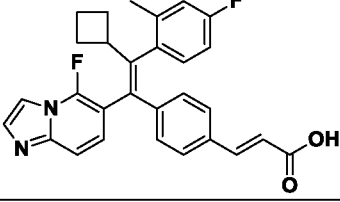
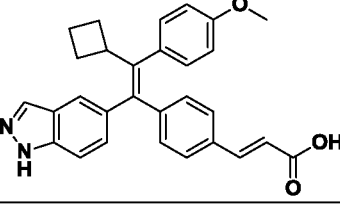
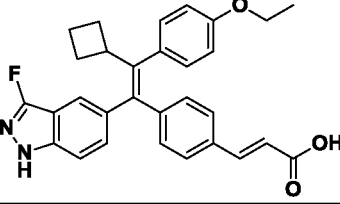
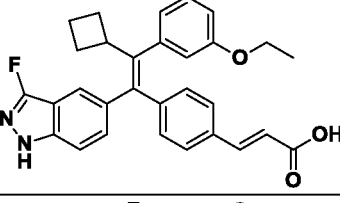
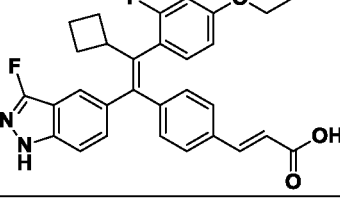
Example	Name	Structure
281	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-(methylsulfonyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
282	(E)-3-(4-((E)-2-(4-Chloro-2-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
283	3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1H-1,2,4-triazol-5(4H)-one	
284	5-((E)-1-(4-((E)-2-(4H-1,2,4-Triazol-3-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	
285	5-((E)-1-(4-((E)-2-(1H-Imidazol-2-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	
286	5-((E)-1-(4-((E)-2-(1H-1,2,3-Triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole	
287	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
288	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	

Example	Name	Structure
289	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(o-tolyl)vinyl)phenyl)acrylic acid	
290	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid	
291	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2,4-difluorophenyl)vinyl)phenyl)acrylic acid	
292	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid	
293	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid	
294	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2,4-dichlorophenyl)vinyl)phenyl)acrylic acid	
295	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid	
296	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	

Example	Name	Structure
297	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
298	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(6-ethoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
299	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	
300	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	
301	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	
302	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid	
303	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
304	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
305	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid	
306	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2,4-difluorophenyl)vinyl)phenyl)acrylic acid	
307	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid	
308	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid	
309	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2,4-dichlorophenyl)vinyl)phenyl)acrylic acid	
310	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid	
311	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
312	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
313	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(6-ethoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
314	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
315	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
316	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
317	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-(2-cyano-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
318	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-fluoro-2-methylphenyl)-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
319	(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
320	(E)-3-(4-((E)-1-(5-Cyanoimidazo[1,2-a]pyridin-6-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid	

Example	Name	Structure
321	(E)-3-(4-((E)-1-(5-Cyanoimidazo[1,2-a]pyridin-6-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid	
322	(E)-3-(4-((E)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-1-(5-cyanoimidazo[1,2-a]pyridin-6-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
323	(E)-3-(4-((E)-2-Cyclobutyl-1-(5-fluoroimidazo[1,2-a]pyridin-6-yl)-2-phenylvinyl)phenyl)acrylic acid	
324	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-fluoro-2-methylphenyl)-1-(5-fluoroimidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
325	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid	
326	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-ethoxyphenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
327	(E)-3-(4-((E)-2-Cyclobutyl-2-(3-ethoxyphenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
328	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-ethoxy-2-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
329	2-(N-((E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acryloyl)sulfamoyl)acetic acid	
330	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(N,N-dimethylsulfamoyl)acrylamide	
331	5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-4-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole	
332	(E)-3-(4-((E)-1-(3-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	
333	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
334	(E)-3-(4-((E)-1-(3-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid	
335	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
336	(E)-3-(4-((E)-1-(3-Cyano-1H-indazol-5-yl)-2-cyclobutyl-2-(5-fluoro-3-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
337	(E)-3-(5-((Z)-2-(2-Chlorophenyl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)pyridin-2-yl)acrylic acid	
338	(E)-3-(5-((Z)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)pyridin-2-yl)acrylic acid	
339	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxypyrimidin-2-yl)vinyl)phenyl)acrylic acid	
340	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)vinyl)phenyl)acrylic acid	
341	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-(trifluoromethyl)pyrimidin-2-yl)vinyl)phenyl)acrylic acid	
342	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-(trifluoromethyl)pyrimidin-4-yl)vinyl)phenyl)acrylic acid	
343	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxy-5-(trifluoromethyl)pyrimidin-4-yl)vinyl)phenyl)acrylic acid	
344	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methoxy-3-(trifluoromethyl)pyrazin-2-yl)vinyl)phenyl)acrylic acid	

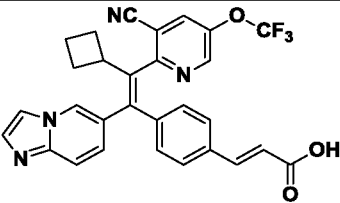
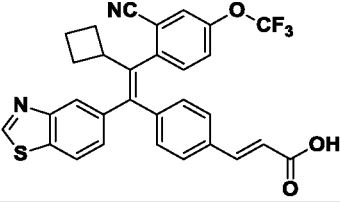
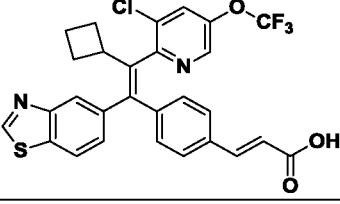
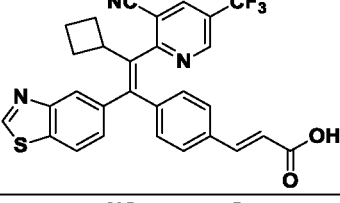
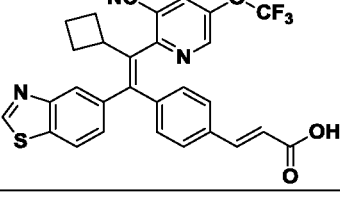
Example	Name	Structure
345	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
346	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
347	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
348	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid	
349	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(6-methoxypyridin-2-yl)vinyl)phenyl)acrylic acid	
350	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid	
351	(E)-3-(4-((E)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid	
352	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
353	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid	
354	(E)-3-(4-((E)-2-Cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)-1-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)vinyl)phenyl)acrylic acid	
355	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)vinyl)phenyl)acrylic acid	
356	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)vinyl)phenyl)acrylic acid	
357	(E)-3-(4-((E)-2-Cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid	
358	(E)-3-(5-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)vinyl)pyridin-2-yl)acrylic acid	
359	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid	
360	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
361	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid	
362	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(2,5-dimethylthiophen-3-yl)vinyl)phenyl)acrylic acid	
363	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2,5-dimethylthiophen-3-yl)vinyl)phenyl)acrylic acid	
364	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3,5-dimethylthiophen-2-yl)vinyl)phenyl)acrylic acid	
365	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(5-cyano-3-methylthiophen-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
366	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid	
367	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid	
368	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-2-yl)-2-cyclopropylvinyl)phenyl)acrylic acid	

Example	Name	Structure
369	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyanobenzo[d]thiazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
370	(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid	
371	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluoro-4-(hydroxymethyl)phenyl)vinyl)phenyl)acrylic acid	
372	(E)-3-(4-((E)-2-(2-Chloro-4-(hydroxymethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
373	(E)-3-(4-((E)-2-Cyclobutyl-2-(3,5-dimethylthiophen-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
374	(E)-3-(4-((E)-2-(5-Cyano-3-methylthiophen-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
375	(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
376	(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
377	(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
378	(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid	
379	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
380	(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
381	(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
382	(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
383	(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
384	(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	

Example	Name	Structure
385	(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid	
386	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-(trifluoromethoxy)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid	
387	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
388	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-cyano-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	
389	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-cyano-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid	

[00292] In some embodiments, there are provided methods of treating an estrogen receptor dependent or estrogen receptor mediated disease or condition in mammal comprising administering to the mammal a therapeutically effective amount of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof. In certain embodiments, the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from cancer, central nervous system (CNS) defects, cardiovascular system defects, hematological system defects, immune and inflammation diseases, susceptibility to infection, metabolic defects, neurological defects, psychiatric defects and reproductive defects. In some embodiments, the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, alcoholism, migraine, aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension, deep vein thrombosis, Graves' Disease, arthritis, multiple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density,

cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, migraine, vertigo, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis, age of menarche, endometriosis, and infertility. In some embodiments, the methods further comprise administering to the mammal radiation therapy. In certain embodiments, the compound of the methods is administered prior to or following surgery. In certain embodiments, the methods comprise administering to the mammal at least one additional anti-cancer agent.

[00293] In some embodiments, there are provided methods of treating cancer in a mammal comprising administering to the mammal a therapeutically effective amount of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cancer is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer. In certain embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is a hormone dependent cancer. In certain embodiments, the cancer is an estrogen receptor dependent cancer. In certain embodiments, the cancer is an estrogen-sensitive cancer. In certain embodiments, the cancer is resistant to anti-hormonal treatment. In certain embodiments, the cancer is an estrogen-sensitive cancer or an estrogen receptor dependent cancer that is resistant to anti-hormonal treatment. In some embodiments, the anti-hormonal treatment includes treatment with at least one agent selected from tamoxifen, fulvestrant, steroidal aromatase inhibitors, and non-steroidal aromatase inhibitors. In some embodiments, the methods further comprise administering to the mammal radiation therapy. In certain embodiments, the compound of the methods is administered prior to or following surgery. In certain embodiments, the methods comprise administering to the mammal at least one additional anti-cancer agent.

[00294] In some embodiments, there are provided methods of treating hormone receptor positive metastatic breast cancer in a postmenopausal woman with disease progression following anti-estrogen therapy comprising administering to the woman an estrogen receptor degrading compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof. In some embodiments, the methods further comprise administering to the mammal radiation therapy. In certain embodiments, the compound of the methods is administered prior to or following surgery. In certain embodiments, the methods comprise administering to the mammal at least one additional anti-cancer agent.

[00295] In some embodiments, there are provided methods of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract in a mammal comprising administering to the mammal an effective amount of a compound described herein (e.g. a compound

of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof. In certain embodiments, the benign or malignant disease is breast cancer. In some embodiments, the methods further comprise administering to the mammal radiation therapy. In certain embodiments, the compound of the methods is administered prior to or following surgery. In certain embodiments, the methods comprise administering to the mammal at least one additional anti-cancer agent.

[00296] In some embodiments, these methods further comprise administering to the mammal at least one additional therapeutic agent selected from abiraterone; abarelix; adriamycin; aactinomycin; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; alemtuzumab; allopurinol; alitretinoin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; aminolevulinic acid; amifostine; amsacrine; anastrozole; anthramycin; aprepitant; arsenic trioxide; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; bendamustine hydrochloride; benzodepa; bevacizumab; bexarotene; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin; bleomycin sulfate; bortezomib; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; capecitabine; cedefingol; cetuximab; chlorambucil; cirolemycin; cisplatin; cladribine; clofarabine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dasatinib; daunorubicin hydrochloride; dactinomycin; darbepoetin alfa; decitabine; degarelix; denileukin diftitox; dexormaplatin; dexrazoxane hydrochloride; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; eltrombopag olamine; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; epoetin alfa; erbulozole; erlotinib hydrochloride; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; everolimus; exemestane; fadrozole hydrochloride; fazarabine; fenretinide; filgrastim; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; fulvestrant; gefitinib; gemcitabine; gemcitabine hydrochloride; gemcitabine –cisplatin; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; imiquimod; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1 a; interferon gamma-1 b; iproplatin; irinotecan hydrochloride; ixabepilone; lanreotide acetate; lapatinib; lenalidomide; letrozole; leuprolide acetate; leucovorin calcium; leuprolide acetate; levamisole; liposomal cytarabine; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; methoxsalen; metoprine; meturedpa; mitindomide; mitocarcin;

mitocromin; mitogillin; mitomalcin; mitomycin C; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nandrolone phenpropionate; nelarabine; nilotinib; nocodazole; nofetumomab; nogalamycin; ofatumumab; oprelvekin; ormaplatin; oxaliplatin; oxisuran; paclitaxel; palifermin; palonosetron hydrochloride; pamidronate; pegfilgrastim; pemetrexed disodium; pentostatin; panitumumab; pazopanib hydrochloride; pemetrexed disodium; plerixafor; pralatrexate; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; quinacrine; raloxifene hydrochloride; rasburicase; recombinant HPV bivalent vaccine; recombinant HPV quadrivalent vaccine; riboprine; rogletimide; rituximab; romidepsin; romiplostim; safinbol; safinbol hydrochloride; sargramostim; semustine; simtrazene; sipuleucel-T; sorafenib; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; sunitinib malate; talisomycin; tamoxifen citrate; tecogalan sodium; tegafur; teloxantrone hydrochloride; temozolomide; temoporfin; temsirolimus; teniposide; teroxirone; testolactone; thalidomide; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; topotecan hydrochloride; toremifene; tositumomab; tositumomab and I¹³¹ Iodine tositumomab; trastuzumab; trestolone acetate; tretinoin; tricyclic phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; valrubicin; vapreotide; verteporfin; vinblastine; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinylicinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorinostat; vorozole; zeniplatin; zinostatin; zoledronic acid; and zorubicin hydrochloride.

Synthesis of Compounds

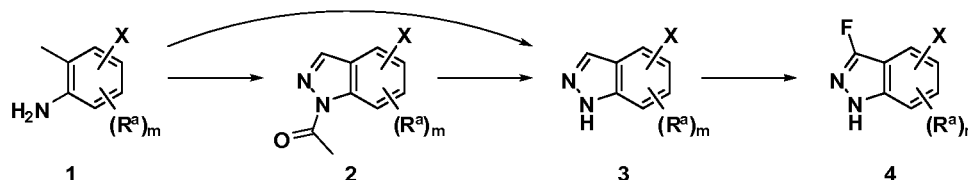
[00297] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. In addition, solvents, temperatures and other reaction conditions presented herein may vary.

[00298] The starting material used for the synthesis of the compounds described herein are either synthesized or obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, and the like. The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein or otherwise known, including those found in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999). General methods for the preparation of compounds is optionally modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein.

[00299] In some embodiments, exemplary compounds described herein are prepared as outlined in the following schemes.

[00300] In some embodiments, 3-fluoroindazoles are prepared as outlined in Scheme 1.

Scheme 1



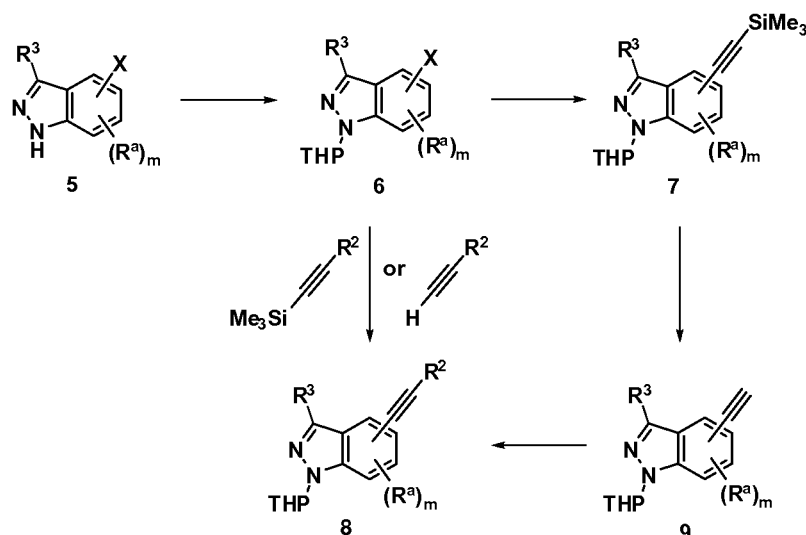
[00301] In some embodiments, a suitable 2-methylaniline compound of Structure 1, where X is a halogen such as bromine or iodine, is reacted with acetic anhydride in a suitable solvent, such as but not limited to toluene, with heating. In some embodiments, the reaction is heated to an internal temperature of about 80-85°C. Isoamyl nitrite is then added to the reaction mixture at a temperature of about 80-90°C to provide indazoles of Structure 2. Indazoles of Structure 2 were then treated with a suitable base in a suitable solvent to provide 1H-indazoles of Structure 3. In some embodiments the suitable base is potassium carbonate. In some embodiments, the suitable solvent is methanol.

[00302] In some other embodiments, a suitable 2-methylaniline compound of Structure 1, is treated with sodium nitrite in a suitable solvent to provide 1H-indazoles of Structure 3. In some embodiments, the suitable solvent is acetic acid.

[00303] In some embodiments, 1H-indazoles of Structure 3 are treated with a fluorinating agent in a suitable solvent to provide 3-fluoroindazoles of Structure 4. In some embodiments, the reaction is carried out under an inert atmosphere, such as but not limited to, an atmosphere of nitrogen. In some embodiments, the reaction is heated. In some embodiments, the reaction is heated to about 60-80°C. In some embodiments, the fluorinating agent is Selectfluor. In some embodiments, the suitable solvent is dimethylacetamide or dimethylformamide. In some other embodiments, the suitable solvent is acetonitrile and acetic acid.

[00304] In some embodiments, suitable indazole compounds are elaborated as outlined in Scheme 2 for the preparation of compounds disclosed herein.

Scheme 2:



[00305] In some embodiments, protection of the acidic proton bearing nitrogen of indazole compounds of Structure 5, where X is a halogen such as bromine or iodine, with a protecting group provides indazole compounds of Structure 6. In some embodiments, the protecting group is tetrahydropyran (THP). In some embodiments, the conditions for nitrogen protection require dihydropyran (DHP), an organic acid and a suitable solvent. In some embodiments, the organic acid is para-toluenesulfonic acid (*p*-TsOH) or pyridinium *p*-toluenesulfonate (PPTS), and the suitable solvent is dichloromethane. In some embodiments, the reaction is performed at room temperature. Other conditions to protect the nitrogen of the starting material are known and include protecting groups such as, but not limited to, methoxymethyl ether (MOM), tert-butyloxycarbonyl (BOC), acetyl (Ac), or triphenylmethyl (trityl). A detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, *Protective Groups*, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure. In some embodiments, the indazoles in Scheme 2 are replaced with analogous azaindazoles, benzothiazoles, benzotriazoles, isoindolinones, benzoxazolones, or imidazopyridines.

[00306] In some embodiments, indazole compounds of Structure 6, where X is a halogen or other suitable leaving group, are coupled with an alkynyl-trimethylsilane or a terminal-alkyne under Sonogashira reaction conditions to provide indazole compounds of Structure 8. In some embodiments, the Sonogashira coupling includes the use of a base, a palladium catalyst, and a copper halide salt in a suitable solvent at elevated temperatures. In some embodiments, suitable bases for this reaction include, but are not limited to, cesium carbonate, potassium carbonate, triethylamine, diethylamine, pyrrolidine, cesium fluoride, or tetrabutylammonium fluoride (TBAF). In some embodiments, suitable palladium catalysts for this reaction include, but are not limited to, Pd(OAc)₂ with dppf, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, or PPh₃; Pd(PPh₃)₄; or PdCl₂(PPh₃)₂. In some embodiments, suitable copper halide salts for this reaction include, but are

not limited, copper iodide. In some embodiments, suitable solvents for this reaction include, but are not limited to, dimethylacetamide, tetrahydrofuran, triethylamine, or pyrrolidine. In some embodiments, suitable elevated temperatures for this reaction include, but are not limited to, about 50-120 °C. In some embodiments, the coupling of an alkynyl-trimethylsilane with indazole compounds of Structure 6 includes the use of Pd(OAc)₂, dppf, CuI, Cs₂CO₃, and dimethylacetamide with heating to about 80-90 °C. In some embodiments, the coupling of a terminal-alkyne with indazole compounds of Structure 6 includes the use of Pd(PPh₃)₂Cl₂, CuI, and triethylamine with the reaction performed at elevated temperatures (e.g. about 80-120 °C). In some other embodiments, when X is iodine, the coupling of an alkynyl-trimethylsilane with indazole compounds of Structure 6 includes the use of TBAF, CuI, Pd(PPh₃)₄, and tetrahydrofuran, with optional heating to about 50 °C. In yet other embodiments, when X is bromine, the coupling of an alkynyl-trimethylsilane with indazole compounds of Structure 6 includes the use of TBAF, CuI, Pd(PPh₃)₄, tetrahydrofuran, and a cosolvent (triethylamine or pyrrolidine) with heating to about 80-120 °C.

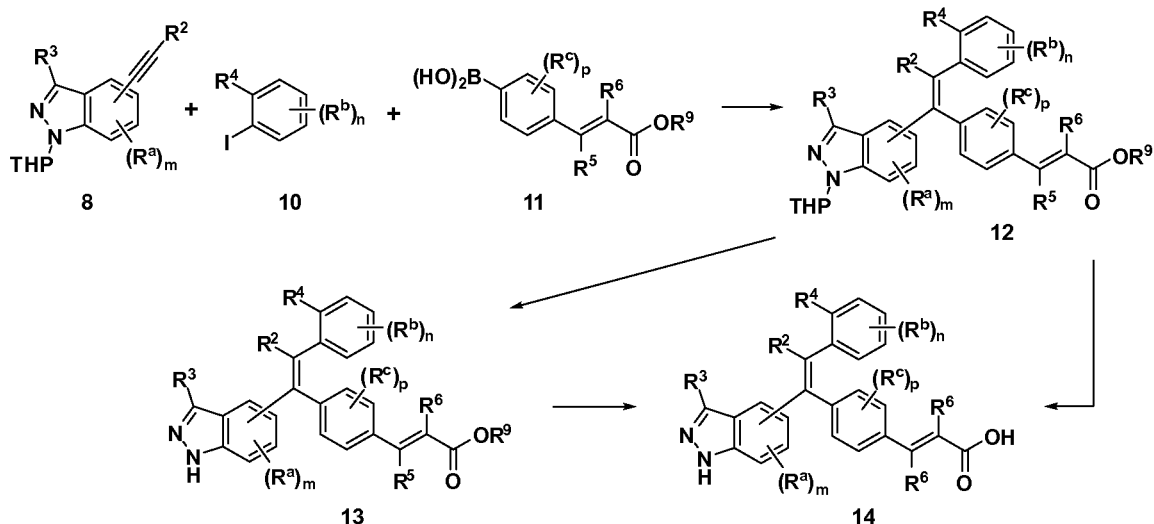
[00307] In some other embodiments, indazole compounds of Structure 6, where X is a halogen or other suitable leaving group, are reacted with a protected acetylene (e.g., trimethylsilylacetylene) under Sonagashira reaction conditions to provide indazole compounds of Structure 7. In some embodiments, the Sonagashira coupling reaction conditions include the use of a palladium catalyst and a copper halide salt. In some embodiments, the Sonagashira reaction conditions includes the use of Pd(Ph₃P)₂Cl₂, CuI, and triethylamine. In one embodiment, the reaction is performed at about 80°C. Other suitable reaction conditions are described in Rafael Chinchilla and Carmen Nájera (2007). Chem. Rev. 107 (3): 874–922.

[00308] The silyl protecting group of indazole compounds of Structure 7 is removed under suitable reaction conditions to provide indazole compounds of Structure 9. In some embodiments, the silyl protecting group is removed with potassium carbonate (K₂CO₃) in methanol. In other embodiments, the silyl protecting group is removed with tetrabutylammoniumfluoride (TBAF) in tetrahydrofuran.

[00309] In some embodiments, indazole compounds of Structure 9 are reacted with R²-X under basic conditions to prepare indazole compounds of Structure 8. In these instances, R² is C₁-C₆alkyl or C₁-C₆fluoroalkyl or C₁-C₄alkoxy or C₁-C₄fluoroalkoxy or C₃-C₆cycloalkyl, or the like, and X is a suitable leaving group. In some embodiments, R² moieties (such as halogen, CN, NO₂, -SR⁹, -S(=O)R¹⁰, -S(=O)₂R¹⁰, -NHS(=O)₂R¹⁰) are installed by other suitable conditions.

[00310] In some embodiments, compounds disclosed herein are prepared as outlined in Scheme 3.

Scheme 3.



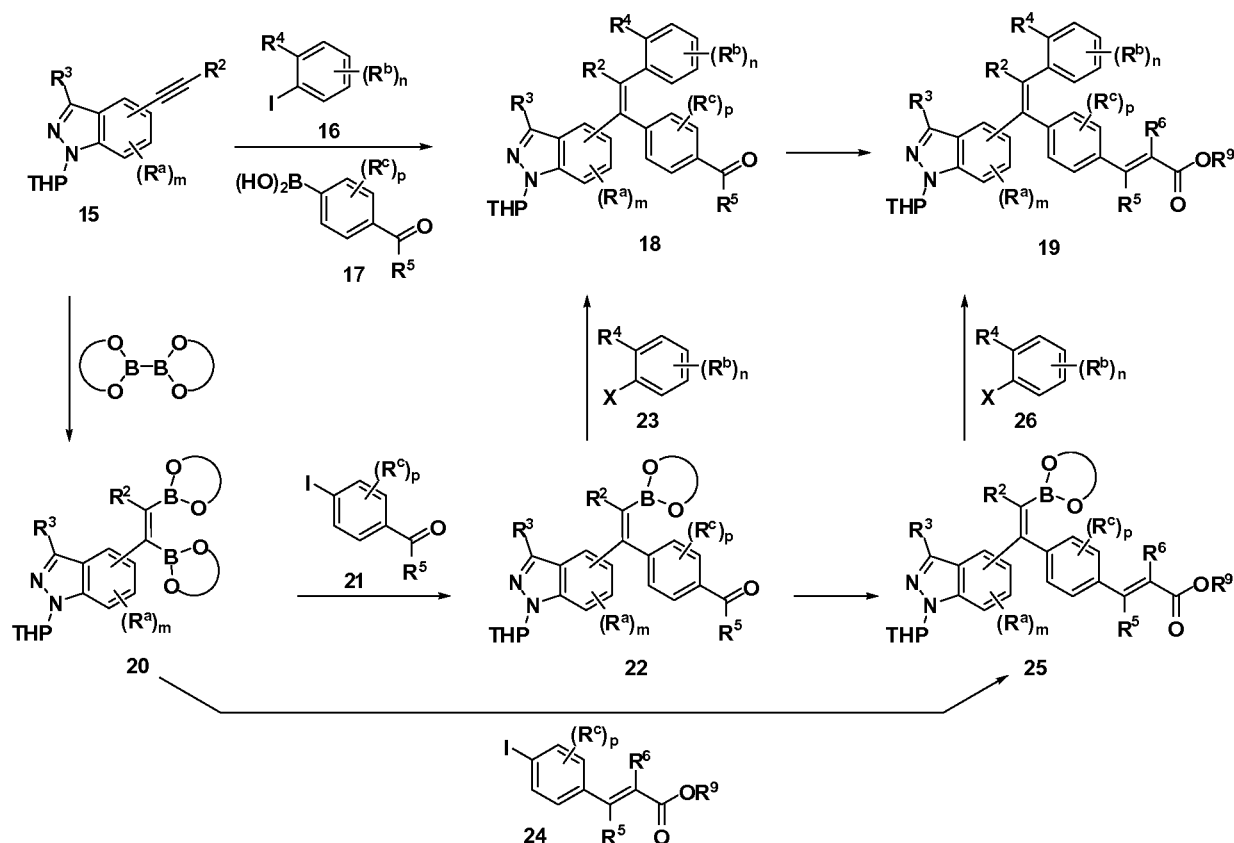
[00311] In some embodiments, indazole compounds of Structure 8, aryl iodides of Structure 10 and aryl boronic acids of Structure 11 are then coupled together under suitable reaction conditions to afford compounds of Structure 12. In some embodiments, indazole compounds of Structure 8 are replaced with analogous azaindazoles, benzothiazoles, benzotriazoles, isoindolinones, benzoxazolones, or imidazopyridines. In some embodiments, aryl iodides of Structure 10 are replaced with analogous pyridine, thiophene, or pyrimidine compounds. In some embodiments, aryl boronic acids of Structure 11 are replaced with analogous pyridine, pyrimidine, or pyrazine compounds. In some embodiments, the suitable reaction conditions include the use of organometallic reagent(s). In some embodiments, the suitable reaction conditions include the use of a palladium catalyst. In some embodiments, the suitable reaction conditions include the use of Pd(PhCN)₂Cl₂, K₂CO₃ in dimethylformamide/water. Other suitable reaction conditions include those described in Chengxiang Zhou and Richard C. Larock, *Journal of Organic Chemistry*, 2005, 70, 3765-3777; Chengxiang Zhou, Daniel E. Emrich, and Richard C. Larock *Organic Letters* 2003, 1579-1582; Tsutomu Konno, Ken-ichi Taku, Takashi Ishihara, *Journal of Fluorine Chemistry* 127 (2006) 966-972.

[00312] The protecting group of compounds of Structure 12 is then removed under suitable reaction conditions to provide compounds of Structure 13. In some embodiments, the suitable reaction conditions include the use of an acid. In some embodiments, the suitable reaction conditions include the use of hydrochloric acid and ethanol with the reaction performed at about 70 °C. In some embodiments, the suitable reaction conditions include the use of hydrochloric acid in dioxane at about 50-80 °C. In some embodiments, the suitable reaction conditions include the use of trifluoroacetic acid in dichloromethane at room temperature. In some embodiments, when R⁹ of compounds of Structure 12 is tert-butyl, treatment of compounds of Structure 12 under some of the foregoing acidic conditions (i.e. hydrochloric acid in dioxane or trifluoroacetic acid in dichloromethane) provides compounds of Structure 14.

[00313] Hydrolysis of the ester group of compounds of Structure **13** provides carboxylic acid compounds of Structure **14**. In some embodiments, the hydrolysis reaction includes the use of lithium hydroxide in a mixture of tetrahydrofuran and ethanol. Other hydrolysis reaction conditions are known.

[00314] In some embodiments, compounds disclosed herein are prepared as outlined in Scheme 4.

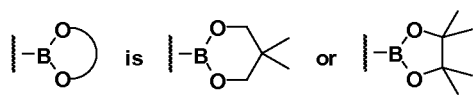
Scheme 4.



[00315] In some embodiments, indazole compounds of Structure **15** are reacted with aryl halides of Structure **16** and boronic acids of Structure **17** under suitable reaction conditions to provide compounds of Structure **18**. In some embodiments, indazole compounds of Structures **15** are replaced with analogous azaindazoles, benzothiazoles, benzotriazoles, isoindolinones, benzoxazolones, or imidazopyridines. In some embodiments, the suitable reaction conditions include the use of organometallic reagent(s). In some embodiments, the suitable organometallic reagent is a palladium catalyst. The aldehyde of compounds of Structure **18** is then transformed to an alkene under suitable reaction conditions to provide compounds of Structure **19**. Suitable reaction conditions include a Horner-Wadsworth-Emmons olefination reaction or a Wittig olefination reaction conditions.

[00316] Alternatively, compounds of Structure **15** are reacted with a borylating agent in the presence of a suitable catalyst and a suitable solvent to provide compounds of Structure **20**. In some

embodiments, the suitable catalyst is an organometallic catalyst. In some embodiments, the suitable catalyst is a platinum catalyst. In some embodiments, the suitable catalyst is $(\eta^2\text{-C}_2\text{H}_4)\text{Pt}(\text{PPh}_3)_2$ or $\text{Pt}(\text{PPh}_3)_4$. Other platinum catalysts are known. In some embodiments,



. In some embodiments, the borylating agent is bis(pinacolato)diboron, or bis(neopentylglycolato)diboron. Suitable solvents include, but are not limited to, dioxane, dimethoxyethane, 2-methyltetrahydrofuran, toluene, and dimethylacetamide. In some embodiments, the reaction is performed under an inert atmosphere. In some embodiments, the reaction is performed under nitrogen. In some embodiments, the reaction is heated, such as for example, to about 80-120 °C.

[00317] A Suzuki cross-coupling is then performed with compounds of Structure **20** and aryl halides of Structure **21** to provide compounds of Structure **22**. In some embodiments, aryl halides of Structure **21** are replaced with analogous pyridine, pyrazine, or pyrimidine compounds. In some embodiments, the Suzuki cross-coupling includes the use a suitable catalyst, a suitable base, and a suitable solvent with optional heating. In some embodiments, the suitable catalysts is a palladium catalyst. Suitable palladium catalysts include but are not limited to, $\text{PdCl}_2(\text{PPh}_3)_2$, and $\text{PdCl}_2(\text{dppf})$. In some embodiments, the suitable base is an inorganic base or an organic base. Suitable bases include, but are not limited to, cesium carbonate, sodium carbonate, potassium carbonate, potassium hydroxide, and sodium hydroxide. Suitable solvents include, but are not limited to, dioxane, dimethoxyethane, 2-methyltetrahydrofuran, toluene, dimethylacetamide, dimethylformamide, and dimethylsulfoxide. In some embodiments the reaction is performed under an inert atmosphere, such as for example, under nitrogen. In some embodiments, the reaction is performed at room temperature. Alternatively the reaction is performed at about 40-50 °C. Other Suzuki reaction conditions are known.

[00318] A subsequent Suzuki cross-coupling is then performed between compounds of Structure **22** and aryl halides of Structure **23** to provide compounds of Structure **18**. In some embodiments, aryl halides of Structure **23** are replaced with analogous thiophene, pyridine, pyrazine, or pyrimidine compounds. In some embodiments, this subsequent Suzuki cross-coupling includes the use a suitable catalyst, a suitable base, and a suitable solvent with heating. Suitable reagents for this subsequent Suzuki cross-coupling reaction include, but are not limited to, those described for the Suzuki cross-coupling between compounds of Structure **20** and aryl halides of Structure **21**. In some embodiments, this subsequent Suzuki cross-coupling is performed at elevated temperatures, such as, for example, about 80-120 °C. Other Suzuki reaction conditions are known.

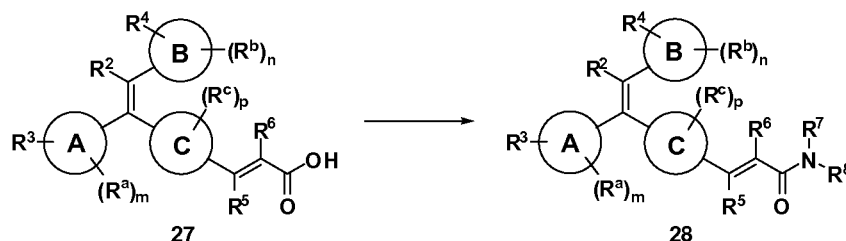
[00319] Alternatively, compounds of Structure **22** are transformed to an alkene under suitable reaction conditions to provide compounds of Structure **25**. In yet an another alternative procedure, a Suzuki cross-coupling is performed with compounds of Structure **20** and aryl halides of Structure **24**

to provide compounds of Structure **25**. In some embodiments, aryl halides of Structure **24** are replaced with analogous pyridine, pyrimidine or pyrazine compounds. Suitable reaction conditions for this Suzuki reaction include, but are not limited to, those conditions described for coupling of compounds of Structure **20** and **21** to provide compounds of Structure **22**. A subsequent Suzuki cross-coupling is then performed between compounds of Structure **25** and aryl halides of Structure **26** to provide compounds of Structure **19**. Suitable reaction conditions for this subsequent Suzuki reaction include, but are not limited to, those conditions described for coupling of compounds of Structure **22** and **23** to provide compounds of Structure **18**.

[00320] Although Schemes 1, 2, 3 and 4 describe the synthesis of indazole compounds, other heteroaryls and rings can be used in place of the indazoles, such as but not limited to azaindazole, benzothiazole, benzotriazole, isoindolinone, benzoxazolone, imidazopyridine. In some embodiments, any one of the phenyl groups may be replaced with a suitable heteroaryl, such as but not limited to pyridine, thiophene, pyrimidine, and pyrazine.

[00321] In some instances, the ester groups of compounds of Structure **19** are converted to other groups in order to prepare compounds of Structure **19** where OR^9 is $NHOH$, NR^7R^8 , $NR^7S(=O)R^8$, $NR^7S(=O)_2R^8$, or $NHC(O)R^8$. In some embodiments, acrylic acid group of compounds described herein are elaborated into acrylamide groups as outlined in Scheme 5.

Scheme 5.



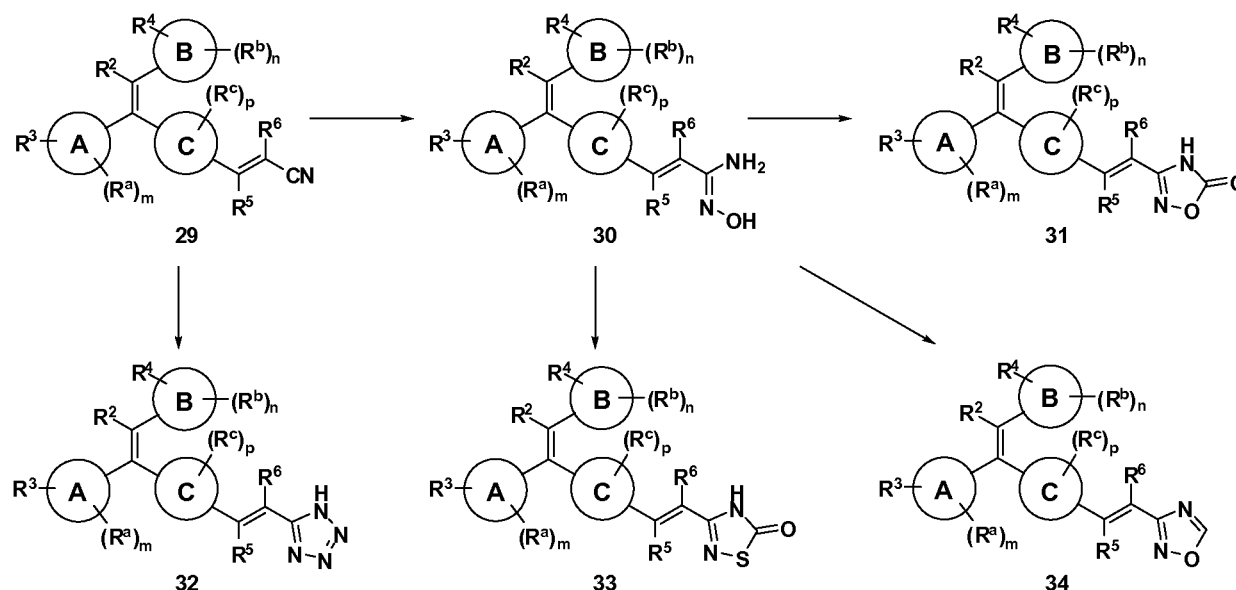
[00322] In some embodiments, acrylic acid compounds of Structure **27** are reacted with a suitable amino containing compound under suitable coupling conditions to form acrylamide compounds of Structure **28**. In some embodiments, the suitable coupling conditions include the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), dimethylaminopyridine, and tetrahydrofuran at room temperature. In some embodiments, the suitable coupling conditions include the use of *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), triethylamine and dichloromethane or dimethylformamide at room temperature. In some embodiments, the suitable coupling conditions include the use of 1,1'-carbonyldiimidazole (CDI), tetrahydrofuran and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature.

[00323] In some embodiments, acrylic acid compounds of Structure **27** are treated with oxalyl chloride in a suitable solvent (such as dichloromethane or tetrahydrofuran) with a catalytic amount of dimethylformamide at room temperature to form the corresponding acid chloride. In some embodiments, the acid chloride is reacted with R^7R^8NH , triethylamine in dioxane or

dichloromethane at 0 °C to provide acrylamide compounds of Structure **28**. In some embodiments, the acid chloride is reacted with R^7R^8NH and potassium carbonate in tetrahydrofuran/water to provide acrylamide compounds of Structure **28**. In some embodiments, the acid chloride is reacted with R^7R^8NH and sodium hydride in dimethylformamide to provide acrylamide compounds of Structure **28**.

[00324] In some embodiments, the compounds described herein include a carboxylic acid bioisostere. In some embodiments, the carboxylic acid bioisosteres are prepared as outlined in Scheme 6.

Scheme 6.

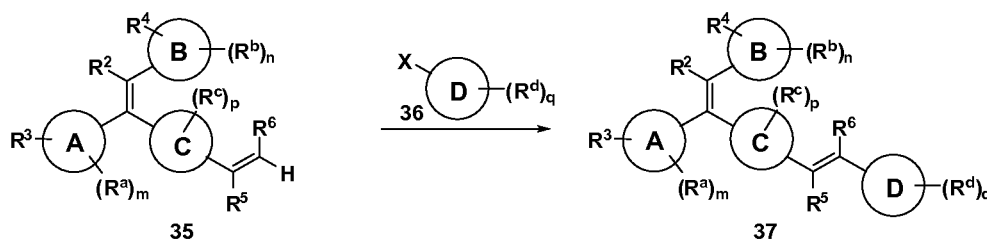


[00325] In some embodiments, acrylonitrile compounds of Structure **29** are prepared as outlined in Schemes 1 to 4 for the acrylic acid compounds. In some embodiments, acrylonitrile compounds of Structure **29** are treated with hydroxylamine hydrochloride, triethylamine, and dimethylsulfoxide at 75 °C for approximately 24 hours to provide compounds of Structure **30**. Alternatively, acrylonitrile compounds of Structure **29** are treated with aqueous hydroxylamine and ethanol, and the reaction is refluxed for approximately 16 hours to provide compounds of Structure **30**. In some embodiments, compounds of Structure **30** are treated with 2-ethylhexylchloroformate at 0 °C for approximately 1 hour and then xylenes at 130 °C for approximately 2 hours to provide compounds of Structure **31**. In alternative embodiments, compounds of Structure **30** are treated with CDI, DBU, and tetrahydrofuran at room temperature for approximately 16 hours to provide compounds of Structure **31**. In some embodiments, compounds of Structure **30** are treated with 1,1'-thiocarbonyldiimidazole (TCDI) and tetrahydrofuran at room temperature for approximately 1 hour and then BF_3 etherate at room temperature for approximately 1 hour to provide compounds of Structure **33**. In some embodiments, compounds of Structure **30** are treated with triethylamine and formic acid in ethyl acetate followed by addition of propylphosphonic anhydride and heating to

about 80 °C to provide compounds of Structure 34. In some embodiments, acrylonitrile compounds of Structure 29 are treated with TMSN_3 , $\text{Bu}_2\text{Sn}(\text{O})$, and toluene at reflux to provide tetrazoles of Structure 32.

[00326] In some embodiments, compounds described herein have the formula of Structure 37 and are prepared as outlined in Scheme 7 (where ring D represents an aryl or heteroaryl ring and R^d is an optional substituent).

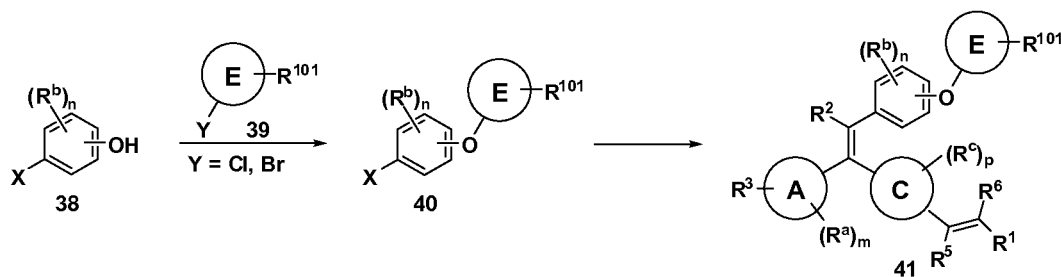
Scheme 7.



[00327] In some embodiments, Heck reaction conditions are used to prepare a compound of Structure 37 from a compound of Structure 35 and an aryl- or heteroaryl-halide of Structure 36 (where X is a halide). In a non-limiting embodiment, a mixture of a compound of Structure 35, an aryl- or heteroaryl-halide of Structure 36, a palladium catalyst, a phosphine ligand, and a suitable base in a suitable solvent are heated to a suitable temperature to provide a compound of Structure 37. For example, in some embodiments, a mixture of a compound of Structure 35, an aryl- or heteroaryl-halide of Structure 36, palladium acetate, Trixiephos, and diethylisopropylamine in acetonitrile are heated to about 80°C for at least 12 hours (i.e. overnight) to provide a compound of Structure 37. Other Heck reaction conditions are known and may be used to prepare compounds of Structure 37 from compounds of Structure 35 and 36.

[00328] In some embodiments, compounds described herein include a R^4 substituent, where R^4 is $-\text{OR}^9$ and R^9 is a substituted or unsubstituted aryl or heteroaryl. In such instances, the $-\text{OR}^9$ substituent is introduced as outlined in Scheme 8 (where ring E represents an aryl or heteroaryl and R^{101} is an optional substituent).

Scheme 8.



[00329] In some embodiments, a $\text{S}_{\text{N}}\text{Ar}$ reaction is used to form the ether compounds of Structure 40 from compounds of Structure 38 (where X is a halide) and compounds of Structure 39 (where Y is a halide such as F, Cl, or Br). In some embodiments, the $\text{S}_{\text{N}}\text{Ar}$ reaction includes the use

of a suitable base in a suitable solvent with optional heating. For example, in some embodiments, the S_NAr reaction includes the use of potassium carbonate or cesium carbonate in tetrahydrofuran, dimethylformamide or dimethylsulfoxide with heating at approximately 70-140 °C. Compounds of Structure **40** are then elaborated into compounds of Structure **41** as described in Schemes 1 to 4.

[00330] In one aspect, compounds described herein are synthesized as outlined in the Examples.

[00331] Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

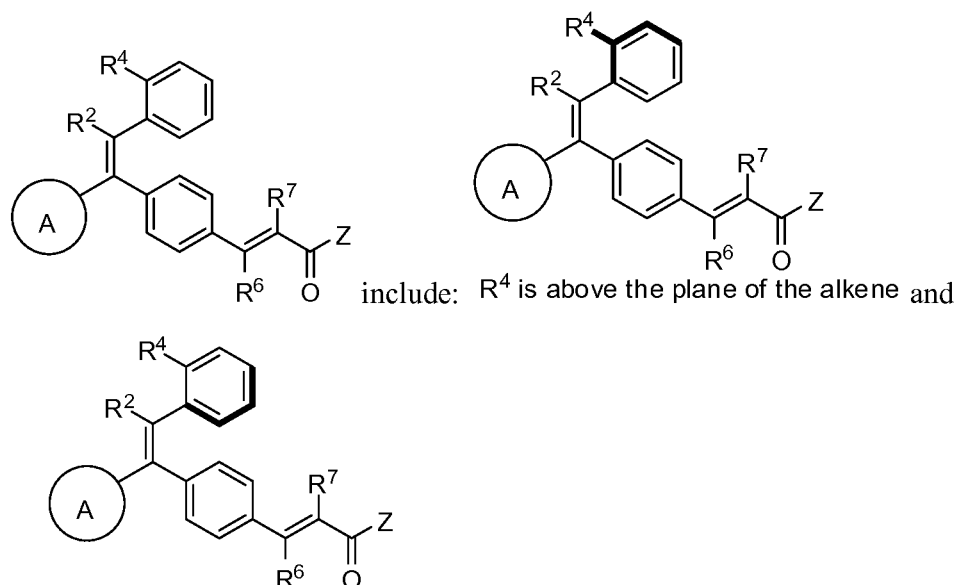
Further Forms of Compounds

[00332] In one aspect, when compounds described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) possess one or more stereocenters then each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00333] Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00334] In certain embodiments, the compounds presented herein are present as atropisomers. Atropisomers refer to stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation allows for the isolation of conformers. Atropisomers display axial chirality. Separation of atropisomers is possible. In some embodiments, separation of atropisomers is possible by chiral resolution methods such as selective crystallization. Atropisomers are optionally characterized by NMR or other suitable characterization means.

[00335] For example, atropisomers of the compound with the structure



[00336] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00337] In some embodiments, compounds described herein are prepared as prodrugs. A “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the “prodrug”) but then is metabolically hydrolyzed to provide the active entity. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00338] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate

esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elsevier, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like. In some embodiments, a carboxyl group is used to provide an ester or amide (i.e. the prodrug), which is then metabolized *in vivo* to provide a carboxylic acid group. In some embodiments, compounds described herein are prepared as alkyl ester prodrugs.

[00339] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds is a prodrug for another derivative or active compound.

[00340] In some embodiments, sites on the aromatic ring portion of compounds described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium or an alkyl group.

[00341] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00342] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F , ^{36}Cl . In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic

advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00343] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00344] “Pharmaceutically acceptable,” as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00345] The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) with acids. Pharmaceutically acceptable salts are also obtained by reacting a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) with a base to form a salt.

[00346] Compounds described herein are optionally formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine,

tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as lysine salts, sodium salts or other suitable amino acid salts. In some embodiments, the compounds provided herein are prepared as a sodium salt. In some embodiments, the compounds provided herein are prepared as an N-methylglucamine salt. In some embodiments, the compounds provided herein are prepared as a hydrochloride salt.

[00347] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound described in Table 1.

[00348] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00349] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts, as well as active metabolites of the compounds described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1) having the same type of activity.

Certain Terminology

[00350] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of “or” or “and” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00351] An “alkyl” group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the “alkyl” group has 1 to 6 carbon atoms (whenever it appears herein, a numerical range such as “1 to 6” refers to each integer in the given

range; *e.g.*, “1 to 6 carbon atoms” means that the alkyl group includes moieties that consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). In one aspect the alkyl is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[00352] “Deuteroalkyl” refers to an alkyl group where 1 or more hydrogen atoms of an alkyl are replaced with deuterium.

[00353] The term “alkenyl” refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula $-C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$ and $-C(CH_3)=CHCH_3$. Depending on the structure, an alkenyl group can be a monoradical or a diradical (*i.e.*, an alkenylene group).

[00354] The term “alkynyl” refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula $-C\equiv C-R$, wherein R refers to the remaining portions of the alkynyl group. Non-limiting examples of an alkynyl group include $-C\equiv CH$, $-C\equiv CCH_3$ and $-C\equiv CCH_2CH_3$. Depending on the structure, an alkynyl group can be a monoradical or a diradical (*i.e.*, an alkynylene group).

[00355] An “alkoxy” group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00356] The term “alkylamine” refers to the $-N(alkyl)_xH_y$ group, where x and y are selected from the group x=1, y=1 and x=2, y=0.

[00357] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. Aromatics are optionally substituted. The term “aromatic” includes both carbocyclic aryl (“aryl”, *e.g.*, phenyl) and heterocyclic aryl (or “heteroaryl” or “heteroaromatic”) groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00358] The term “carbocyclic” or “carbocycle” refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic.

[00359] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups are optionally substituted. In one aspect, an aryl is a phenyl or a naphthalenyl. In one aspect, an aryl is a phenyl. In one aspect, an aryl is a C_6 - C_{10} aryl. Depending on the structure, an aryl group is optionally a monoradical or a diradical (*i.e.*, an arylene group).

[00360] The term “cycloalkyl” refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom.

Cycloalkyls include moieties that are saturated, or partially unsaturated. Cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Cycloalkyl groups are optionally substituted or unsubstituted. In one aspect, a cycloalkyl is a C₃-C₆cycloalkyl.

[00361] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo.

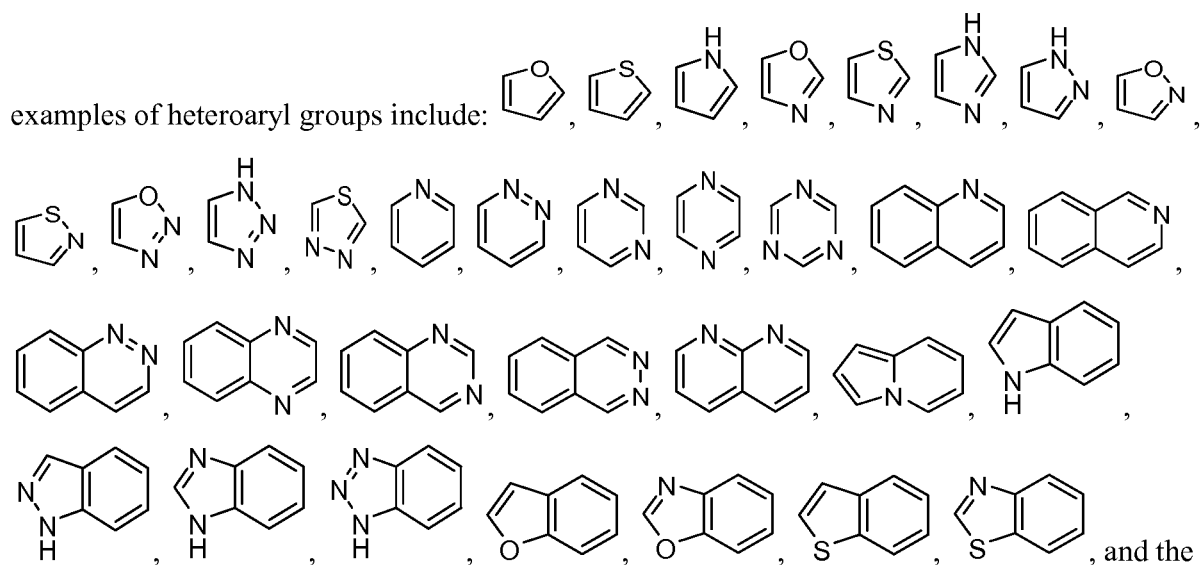
[00362] The term “fluoroalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C₁-C₆fluoroalkyl.

[00363] The term “heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* -NH-, -N(alkyl)-, sulfur, or combinations thereof. In one aspect, a heteroalkyl is a C₁-C₆heteroalkyl.

[00364] The term “heterocycle” or “heterocyclic” refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl. An example of a 4-membered heterocyclic group is azetidiny. An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinoliziny. Examples of aromatic heterocyclic groups are

pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxaliny, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or N-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[00365] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative



like. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl is a monocyclic or bicyclic heteroaryl. In some embodiments, heteroaryl is a C₁-C₉heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₅heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C₆-C₉heteroaryl. Depending on the structure, a heteroaryl group is optionally a monoradical or a diradical (i.e., a heteroarylene group).

[00366] A “heterocycloalkyl” or “heteroalicyclic” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, a heterocycloalkyl is fused with a phenyl or monocyclic heteroaryl. In some embodiments, a heterocycloalkyl is fused with a phenyl or monocyclic heteroaryl and the point of attachment to the rest of the molecule is through a carbon atom of the fused phenyl or fused monocyclic heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C₂-C₁₀heterocycloalkyl. In another aspect, a heterocycloalkyl is a C₄-C₁₀heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 O atoms and 0-1 S atoms in the ring.

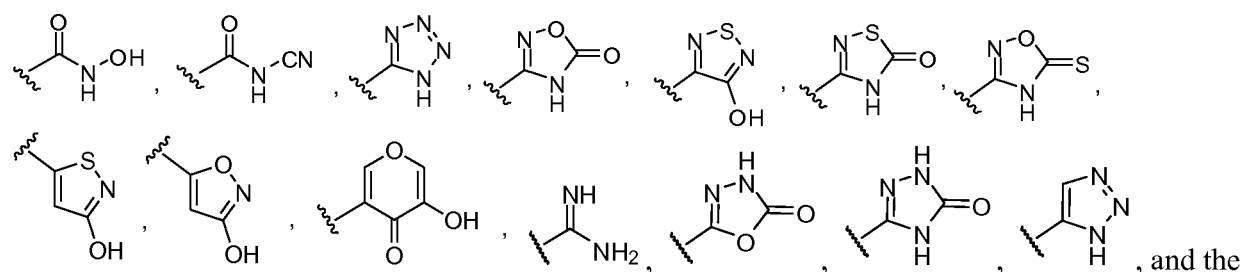
[00367] “Aza” when added to the name of a heterocyclic ring, denotes that the ring includes 1 or 2 additional N atoms in the heterocyclic ring.

[00368] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00369] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00370] The term “carboxylic acid bioisostere” refers to a functional group or moiety that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety.

Examples of carboxylic acid bioisosteres include, but are not limited to,



[00371] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio,

alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, nitro, haloalkyl, fluoroalkyl, fluoroalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. In some embodiments, optional substituents are independently selected from halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CF₃, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, and -CH₂OH. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) includes oxo (=O).

[00372] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00373] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00374] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist. In some embodiments, a modulator is a degrader.

[00375] “Selective estrogen receptor modulator” or “SERM” as used herein, refers to a molecule that differentially modulates the activity of estrogen receptors in different tissues. For example, in some embodiments, a SERM displays ER antagonist activity in some tissues and ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in some tissues and minimal or no ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in breast tissues, ovarian tissues, endometrial tissues, and/or cervical tissues but minimal or no ER agonist activity in uterine tissues.

[00376] The term “antagonist” as used herein, refers to a small -molecule agent that binds to a nuclear hormone receptor and subsequently decreases the agonist induced transcriptional activity of the nuclear hormone receptor.

[00377] The term “agonist” as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently increases nuclear hormone receptor transcriptional activity in the absence of a known agonist.

[00378] The term “inverse agonist” as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently decreases the basal level of nuclear hormone receptor transcriptional activity that is present in the absence of a known agonist.

[00379] The term “degrader” as used herein, refers to a small molecule agent that binds to a nuclear hormone receptor and subsequently lowers the steady state protein levels of said receptor. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%.

[00380] The term “selective estrogen receptor degrader” or “SERD” as used herein, refers to a small molecule agent that preferentially binds to estrogen receptors versus other receptors and subsequently lowers the steady state estrogen receptor levels.

[00381] The term “ER-dependent”, as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogen receptors.

[00382] The term “ER-mediated”, as used herein, refers to diseases or conditions that would not occur in the absence of estrogen receptors but can occur in the presence of estrogen receptors.

[00383] The term “ER-sensitive”, as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogens.

[00384] The term “cancer” as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

[00385] Additional non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer,

ependymblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenström macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

[00386] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00387] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a

clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00388] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00389] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00390] The terms “kit” and “article of manufacture” are used as synonyms.

[00391] A “metabolite” of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term “active metabolite” refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term “metabolized,” as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00392] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates

such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00393] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Routes of Administration

[00394] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00395] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00396] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Dekker, New York, N.Y., 1980; and Pharmaceutical Dosage

Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00397] In some embodiments, there are provided a pharmaceutical composition comprising a therapeutically effective amount of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof.

[00398] Provided herein are pharmaceutical compositions that include a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the compounds described herein are administered as pharmaceutical compositions in which a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with other active ingredients, as in combination therapy. In other embodiments, the pharmaceutical compositions include other medicinal or pharmaceutical agents, carriers, adjuvants, preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In yet other embodiments, the pharmaceutical compositions include other therapeutically valuable substances.

[00399] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, with other chemical components (i.e. pharmaceutically acceptable inactive ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to a mammal.

[00400] A therapeutically effective amount depends, inter alia, on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds are optionally used singly or in combination with one or more therapeutic agents as components of mixtures.

[00401] The pharmaceutical formulations described herein are administered to a subject by appropriate administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations,

pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00402] Pharmaceutical compositions including a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00403] The pharmaceutical compositions will include at least one compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides (if appropriate), crystalline forms, amorphous phases, as well as active metabolites of these compounds having the same type of activity. In some embodiments, compounds described herein exist in unsolvated form or in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00404] The pharmaceutical compositions described herein, which include a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, are formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solid oral dosage forms, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00405] In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[00406] Pharmaceutical preparations that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some embodiments, the push-fit capsules do not include any other ingredient besides the capsule shell and the active ingredient. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00407] All formulations for oral administration are in dosages suitable for such administration.

[00408] In one aspect, solid oral dosage forms are prepared by mixing a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, with one or more of the following: antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00409] In some embodiments, the solid dosage forms disclosed herein are in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder, a capsule, solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, beads, pellets, granules. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulation is in the form of a capsule.

[00410] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutical excipients to form a bulk blend composition. The bulk blend is readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. In some embodiments, the individual unit dosages include film coatings. These formulations are manufactured by conventional formulation techniques.

[00411] Conventional formulation techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00412] In some embodiments, tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating provides a delayed release of the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry[®] coatings or sugar coating). Film coatings including Opadry[®] typically range from about 1% to about 3% of the tablet weight.

[00413] A capsule is prepared, for example, by placing the bulk blend of the formulation of the compound described above, inside of a capsule. In some embodiments, the formulations (non-

aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule is swallowed whole or the capsule is opened and the contents sprinkled on food prior to eating.

[00414] In various embodiments, the particles of the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00415] In still other embodiments, effervescent powders are also prepared. Effervescent salts have been used to disperse medicines in water for oral administration.

[00416] In some embodiments, the pharmaceutical solid oral dosage forms are formulated to provide a controlled release of the active compound. Controlled release refers to the release of the active compound from a dosage form in which it is incorporated according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00417] In some embodiments, the solid dosage forms described herein are formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine or large intestine. In one aspect, the enteric coated dosage form is a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. In one aspect, the enteric coated oral dosage form is in the form of a capsule containing pellets, beads or granules.

[00418] Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00419] In other embodiments, the formulations described herein are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Exemplary pulsatile dosage forms and methods of their manufacture are disclosed in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, 5,840,329 and 5,837,284. In one embodiment, the pulsatile dosage form includes at least two groups of particles, (i.e. multiparticulate) each containing the formulation described herein. The first group of particles provides a substantially immediate dose of the active compound upon ingestion by a mammal. The first group of particles is either uncoated or include a coating and/or sealant. In one aspect, the second group of particles comprises coated particles. The coating on the second group of particles provides a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings for pharmaceutical compositions are described herein or in the art.

[00420] In some embodiments, pharmaceutical formulations are provided that include particles of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and at least one dispersing agent or suspending agent for oral administration to a subject. In some embodiments, the formulations are a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00421] In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh *et al.*, Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002). In addition to the particles of the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, the liquid dosage forms include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions further include a crystalline inhibitor.

[00422] Buccal formulations that include a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, are administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136. In addition, the buccal dosage forms described herein

optionally further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. For buccal or sublingual administration, the compositions optionally take the form of tablets, lozenges, or gels formulated in a conventional manner.

[00423] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is prepared part of a transdermal dosage form. In one embodiment, the transdermal formulations described herein include at least three components: (1) a formulation of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof; (2) a penetration enhancer; and (3) an aqueous adjuvant. In some embodiments the transdermal formulations include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation further includes a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein maintain a saturated or supersaturated state to promote diffusion into the skin.

[00424] In one aspect, formulations suitable for transdermal administration of compounds described herein employ transdermal delivery devices and transdermal delivery patches and include lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In one aspect, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein is accomplished by means of iontophoretic patches and the like. In one aspect, transdermal patches provide controlled delivery of the active compound. In one aspect, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00425] In one aspect, a compound of described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In one aspect, formulations suitable for intramuscular, subcutaneous, or intravenous injection include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), vegetable oils and organic esters, such as ethyl oleate. In some embodiments, formulations suitable for subcutaneous injection contain additives such as preserving,

wetting, emulsifying, and dispensing agents. Prolonged absorption of the injectable pharmaceutical form is optionally brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00426] For intravenous injections, compounds described herein are formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

[00427] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are known.

[00428] Parenteral injections involve either bolus injection and/or continuous infusion. Formulations for injection are optionally presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. In some embodiments, the pharmaceutical composition described herein are in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In one aspect, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00429] In certain embodiments, delivery systems for pharmaceutical compounds are employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein also optionally include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00430] In some embodiments, the compounds described herein are administered topically and are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Methods of Dosing and Treatment Regimens

[00431] In one embodiment, the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from a reduction of estrogen receptor activity. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt, active

metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00432] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00433] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound of described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00434] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00435] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00436] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved

disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00437] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00438] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00439] In one embodiment, the daily dosages appropriate for the compound of described herein (*e.g.* a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, described herein are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00440] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ and the ED₅₀. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD₅₀ and ED₅₀. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00441] In certain instances, it is appropriate to administer at least one compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents. In certain embodiments, the pharmaceutical composition further comprises one or more anti-cancer agents.

[00442] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00443] In one specific embodiment, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00444] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is simply be additive of the two therapeutic agents or the patient experiences a synergistic benefit.

[00445] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens is optionally determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic dosing, *i.e.*, providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of

treatment with the second agent. It also includes treatments in which a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00446] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease, disorder or condition from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00447] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00448] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[00449] The compounds described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

Exemplary Agent for use in Combination Therapy

[00450] In some embodiments, methods for treatment of estrogen receptor-dependent or estrogen receptor-mediated conditions or diseases, such as proliferative disorders, including cancer, comprises administration to a mammal a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent.

[00451] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in combination with hormone blocking therapy, chemotherapy, radiation therapy, monoclonal antibodies, or combinations thereof.

[00452] Hormone blocking therapy includes the use of agents that block the production of estrogens or block the estrogen receptors. In some embodiments, hormone blocking therapy includes the use of estrogen receptor modulators and/ aromatase inhibitors. Estrogen receptor modulators include triphenylethylene derivatives (e.g. tamoxifen, toremifene, droloxifene, 3-hydroxytamoxifen, idoxifene, TAT-59 (a phosphorylated derivative of 4- hydroxytamoxifen) and GW5638 (a carboxylic acid derivative of tamoxifen)); non-steroidal estrogen receptor modulators (e.g. raloxifene, LY353381 (SERM3) and LY357489); steroidal estrogen receptor modulators (e.g. ICI-182,780). Aromatase inhibitors include steroidal aromatase inhibitors and non-steroidal aromatase inhibitors. Steroidal aromatase inhibitors include, but are not limited to, such exemestane. Non-steroidal aromatase inhibitors include, but are not limited to, as anastrozole, and letrozole.

[00453] Chemotherapy includes the use of anti-cancer agents.

[00454] Monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin).

[00455] In some embodiments, the at least one additional therapeutic agent for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, includes one or more of the following: abiraterone; abarelix; adriamycin; actinomycin; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; alemtuzumab; allopurinol; alitretinoin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; aminolevulinic acid; amifostine; amsacrine; anastrozole; anthramycin; aprepitant; arsenic trioxide; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; bendamustine hydrochloride; benzodepa; bevacizumab; bexarotene; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin; bleomycin sulfate; bortezomib; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; capecitabine; cedefingol; cetuximab; chlorambucil; cirolemycin; cisplatin; cladribine; clofarabine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dasatinib;

daunorubicin hydrochloride; dactinomycin; darbepoetin alfa; decitabine; degarelix; denileukin diftitox; dexormaplatin; dexrazoxane hydrochloride; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitucin; eltrombopag olamine; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; epoetin alfa; erbulozole; erlotinib hydrochloride; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; everolimus; exemestane; fadrozole hydrochloride; fazarabine; fenretinide; filgrastim; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; fulvestrant; gefitinib; gemcitabine; gemcitabine hydrochloride; gemcitabine –cisplatin; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; imiquimod; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1 a; interferon gamma-1 b; iproplatin; irinotecan hydrochloride; ixabepilone; lanreotide acetate; lapatinib; lenalidomide; letrozole; leuprolide acetate; leucovorin calcium; leuprolide acetate; levamisole; liposomal cytarabine; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; methoxsalen; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin C; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nandrolone phenpropionate; nelarabine; nilotinib; nocodazole; nofetumomab; nogalamycin; ofatumumab; oprelvekin; ormaplatin; oxaliplatin; oxisuran; paclitaxel; palifermin; palonosetron hydrochloride; pamidronate; pegfilgrastim; pemetrexed disodium; pentostatin; panitumumab; pazopanib hydrochloride; pemetrexed disodium; plerixafor; pralatrexate; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; quinacrine; raloxifene hydrochloride; rasburicase; recombinant HPV bivalent vaccine; recombinant HPV quadrivalent vaccine; riboprime; rogletimide; rituximab; romidepsin; romiplostim; safingol; safingol hydrochloride; sargramostim; semustine; simtrazene; sipuleucel-T; sorafenib; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; sunitinib malate; talisomycin; tamoxifen citrate; tecogalan sodium; tegafur; teloxantrone hydrochloride; temozolomide; temoporphin; temsirolimus; teniposide; teroxirone; testolactone; thalidomide; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; topotecan hydrochloride; toremifene; tositumomab and I 131 Iodine tositumomab; trastuzumab; trestolone acetate; tretinoin; tricitabine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride;

uracil mustard; uredepa; valrubicin; vapreotide; verteporfin; vinblastine; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinatate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorinostat; vorozole; zeniplatin; zinostatin; zoledronic acid; and zorubicin hydrochloride.

[00456] In some embodiments, the at least one additional chemotherapeutic agent is selected from, by way of example only, alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00457] In one aspect, the compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered or formulated in combination with one or more anti-cancer agents. In some embodiments, one or more of the anti-cancer agents are proapoptotic agents. Examples of anti-cancer agents include, but are not limited to, any of the following: gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, or PD184352, paclitaxel, and analogs of paclitaxel. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules and are optionally useful for treating cancer in combination with the compounds described herein.

[00458] Further examples of anti-cancer agents for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, include inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).

[00459] Further examples of anti-cancer agents for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, include aromatase

inhibitors. Aromatase inhibitors include steroidal aromatase inhibitors and non-steroidal aromatase inhibitors. Steroidal aromatase inhibitors include, but are not limited to, exemestane. Non-steroidal aromatase inhibitors include, but are not limited to, anastrozole, and letrozole.

[00460] Yet other anticancer agents for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, include alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, etc.), or triazenes (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[00461] Examples of natural products for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha).

[00462] Examples of alkylating agents for use in combination with a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, include, but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazenes (decarbazine, etc.).

[00463] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used to treat cancer in combination with: a second antiestrogen (e.g., tamoxifen), an antiandrogen (e.g., bicalutamide, flutamide), a gonadotropin releasing hormone analog (e.g., leuprolide).

[00464] Other agents that are optionally used in the methods and compositions described herein for the treatment or prevention of cancer include platinum coordination complexes (e.g., cisplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procabazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide).

[00465] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules include without limitation the following marketed drugs and drugs in

development: Erbulozole, Dolastatin 10, Mivobulin isethionate, Vincristine, NSC-639829, Discodermolide, ABT-751, Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride, Epothilones (such as Epothilone A, Epothilone B, Epothilone C, Epothilone D, Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B, 21-hydroxyepothilone D, 26-fluoroepothilone, Auristatin PE, Soblidotin, Vincristine sulfate, Cryptophycin 52, Vitilevuamide, Tubulysin A, Canadensol, Centaureidin, Oncocidin A1 Fijianolide B, Laulimalide, Narcosine, Nascapine, Hemiasterlin, Vanadocene acetylacetonate, Indanocine Eleutherobins (such as Desmethyleleutherobin, Desaetyeleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (-)-Phenylahistin, Myoseverin B, Resverastatin phosphate sodium.

[00466] In one aspect, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is co-administered with thrombolytic agents (e.g., alteplase anistreplase, streptokinase, urokinase, or tissue plasminogen activator), heparin, tinzaparin, warfarin, dabigatran (e.g., dabigatran etexilate), factor Xa inhibitors (e.g., fondaparinux, draparinux, rivaroxaban, DX-9065a, otamixaban, LY517717, or YM150), ticlopidine, clopidogrel, CS-747 (prasugrel, LY640315), ximelagatran, or BIBR 1048.

[00467] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used in combination with anti-emetic agents to treat nausea or emesis, which result from the use of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, anti-cancer agent(s) and/or radiation therapy.

[00468] Anti-emetic agents include, but are not limited to: neurokinin-1 receptor antagonists, 5HT₃ receptor antagonists (such as ondansetron, granisetron, tropisetron, palonosetron, and zatisetron), GABA_B receptor agonists (such as baclofen), corticosteroids (such as dexamethasone, prednisone, prednisolone, or others), dopamine antagonists (such as, but not limited to, domperidone, droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, metoclopramide), antihistamines (H₁ histamine receptor antagonists, such as but not limited to, cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, hydroxyzine), cannabinoids (such as but not limited to, cannabis, marinol, dronabinol), and others (such as, but not limited to, trimethobenzamide; ginger, emetrol, propofol).

[00469] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a

pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin- α).

[00470] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of neutropenia. Examples of agents useful in the treatment of neutropenia include, but are not limited to, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00471] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered with corticosteroids. Corticosteroids, include, but are not limited to: betamethasone, prednisone, alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocortal, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, and ulobetasol.

[00472] In one embodiment, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is administered to a mammal in combination with a non-steroidal anti-inflammatory drug (NSAID). NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398).

[00473] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is coadministered with an analgesic.

[00474] In some embodiments, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is used in combination with radiation therapy (or radiotherapy). Radiation therapy is the treatment of cancer and other diseases with ionizing radiation. Radiation therapy is optionally used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, prostate, colon, uterus and/or cervix. It is also optionally used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

[00475] A technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy (brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) Using internal radiotherapy, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, prostate, colon, and cervix.

[00476] The term “radiotherapy” or “ionizing radiation” include all forms of radiation, including but not limited to α , β , and γ radiation and ultraviolet light.

Kits/Articles of Manufacture

[00477] For use in the therapeutic methods of use described herein, kits and articles of manufacture are also described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[00478] The articles of manufacture contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that would benefit by antagonism of androgen receptors.

[00479] For example, the container(s) include a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, optionally in a composition or in combination with another agent as disclosed herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[00480] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00481] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

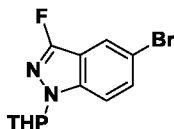
[00482] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

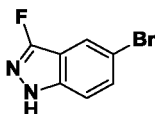
[00483] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Intermediate 1

5-Bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



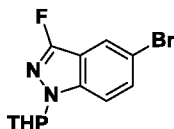
Step 1: 5-Bromo-3-fluoro-1H-indazole



[00484] Selectfluor (72 g, 203 mmol) was added to a solution of 5-bromo-1H-indazole (20.0 g, 102 mmol) and *N,N*-dimethylacetamide (500 mL) under N₂. The mixture was heated at 60 °C for

18 h, allowed to cool to rt, diluted with ethyl acetate (1.5 L), and washed with water (150 mL $\times$ 3). The organic layer was dried (Na₂SO₄), filtered, concentrated, and purified by silica gel chromatography (1:10; ethyl acetate:petroleum ether) to give 10.8 g of an impure product. Repurification by silica gel chromatography (1:20; ethyl acetate:petroleum ether) gave 9 g of 5-bromo-3-fluoro-1*H*-indazole as a light yellow solid. ¹H NMR (400 MHz; DMSO-*d*₆): δ 12.77 (s, 1H), 7.96 (s, 1H), 7.54 (d, 1H), 7.48 (d, 1H).

Step 2: 5-Bromo-3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole



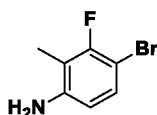
[00485] A mixture of 5-bromo-3-fluoro-1*H*-indazole (9.5 g, 44.2 mmol), *p*-toluenesulfonic acid (840 mg, 4.4 mmol), 3,4-dihydro-2*H*-pyran (4.83 g, 57.5 mmol), and dichloromethane (150 mL) was stirred at rt for 18 h, diluted with dichloromethane (200 mL), and then washed with water (150 mL). The organic layer was dried (Na₂SO₄), filtered, concentrated, and purified by silica gel chromatography (1:100 $\rightarrow$ 1:50; ethyl acetate/petroleum ether) to give 11 g of 5-bromo-3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.96 (s, 1H), 7.70 (d, 1H), 7.60 (d, 1H), 5.76 (dd, 1H), 3.84-3.80 (m, 1H), 3.71-3.64 (m, 1H), 2.20-2.15 (m, 1H), 1.97-1.87 (m, 2H), 1.69-1.64 (m, 1H), 1.53-1.47 (m, 2H).

Intermediate 2

5-Bromo-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole



Step 1: 4-Bromo-3-fluoro-2-methylaniline



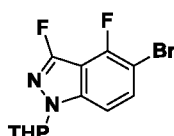
[00486] To a solution of 3-fluoro-2-methylaniline (20 g, 0.16 mol) in CH₃CN (500 mL) was added NBS (31.3 g, 0.176 mol) in portions at 10 °C. The resulting mixture was stirred at room temperature for 30 minutes. Upon completion, saturated Na₂S₂O₃ (500 mL) was added slowly into the reaction mixture at 10 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was washed with petroleum ether affording the title compound (20 g), which was used in the next step without further purification. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.08 (t, 1H), 6.40 (dd, 1H), 5.35 (br, 2H), 1.98 (d, 3H).

Step 2: 5-Bromo-4-fluoro-1H-indazole

[00487] To a solution of 4-bromo-3-fluoro-2-methylaniline (20 g, 98.0 mmol) in $\text{CH}_3\text{CO}_2\text{H}$ (600 mL) was added NaNO_2 (8.1 g, 118 mmol) at 10 °C. The resulting mixture was stirred at room temperature for 4 hours. Upon completion, aqueous NaOH (50%) was added to the reaction mixture until pH was ~7-8. The mixture was extracted with EtOAc . The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (0~40% EtOAc in petroleum ether) affording the title compound (16 g). ^1H NMR (300 MHz, DMSO-d_6): δ 13.58 (br, 1H), 8.22 (s, 1H), 7.53 (t, 1H), 7.38 (d, 1H).

Step 3: 5-Bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00488] To a mixture of 5-bromo-4-fluoro-1H-indazole (50 g, 0.23 mol) and 3,4-dihydro-2H-pyran (23 g, 0.28 mol) in dry dichloromethane (1000 mL) was added p-TsOH (2.2 g, 11.5 mmol) at room temperature. The resulting mixture was stirred overnight at that temperature. Upon completion, saturated aqueous NaHCO_3 (100 mL) was added slowly into the reaction mixture. The organic layer was separated, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (0~2 % EtOAc in petroleum ether) and then re-crystallized from petroleum ether to afford the title compound (55 g). ^1H NMR (300 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.58-7.66 (m, 2H), 5.89 (dd, 1H), 3.90-3.85 (m, 1H), 3.79-3.70 (m, 1H), 2.42-2.29 (m, 1H), 2.06-1.94 (m, 2H), 1.77-1.68 (m, 1H), 1.60-1.53 (m, 2H); LCMS: 299 ($\text{M}+\text{H}$)⁺.

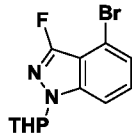
Intermediate 3**5-Bromo-3,4-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole**

[00489] A suspension of Selectfluor (10.5 g, 29.7 mmol) in DMF (30 mL) was added dropwise to a solution of 5-bromo-4-fluoro-1H-indazole (5.15 g, 24.0 mmol, Intermediate 2, Step 2) in DMF (10 mL) at 60 °C under N_2 . The resulting mixture was heated at 60 °C for 18 hours. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (3x90 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography on silica gel (1:10 EA/PE) to give 5-bromo-3,4-difluoro-1H-

indazole as a yellow solid (1.13 g). ^1H NMR (400 MHz, CDCl_3): δ 9.72 (s, 1H), 7.52 (dd, 1H), 7.16 (dd, 1H). Following General Procedure A, 5-Bromo-3,4-difluoro-1*H*-indazole gave 5-bromo-3,4-difluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole: ^1H NMR (400 MHz, CDCl_3): δ 7.49 (dd, 1H), 7.22 (dd, 1H), 5.56 (dd, 1H), 3.99-3.55 (m, 1H), 3.73-3.67 (m, 1H), 2.45-2.36 (m, 1H), 2.16-2.22 (m, 2H), 1.76-1.63 (m, 3H).

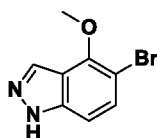
[00490] The Intermediate in Table 2 was prepared from 4-bromoindazole following the procedure outlined for Intermediate 3.

Table 2.

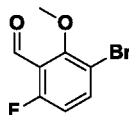
Intermediate 4	4-Bromo-3-fluoro-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	
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Intermediate 5

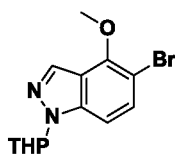
5-Bromo-4-methoxy-1*H*-indazole



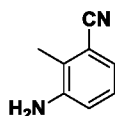
Step 1: 3-Bromo-6-fluoro-2-methoxybenzaldehyde



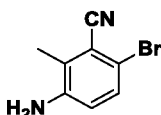
[00491] Diisopropylamine (9.6 mL, 69 mmol) was dissolved in THF (100 mL) under nitrogen atmosphere. The solution was cooled to -78 °C, and *n*-BuLi (21.6 mL, 2.5M in hexanes) was added over 10 min. The resulting solution was stirred at -78 °C for an additional 20 min. Then, a solution of 1-bromo-4-fluoro-2-methoxybenzene (10 g, 49 mmol) in THF (20 mL) was added dropwise over 15 min. The mixture was stirred at -78 °C for 1 hour. DMF (4.2 mL, 54 mmol) was added dropwise over 5 min, and the reaction mixture was stirred at -78 °C for another 45 min. Saturated aqueous NH_4Cl (50 mL) was added, and the mixture was allowed to warm to room temperature and then diluted with Et_2O (200 mL) and 2N HCl (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2x50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography on silica gel (1:50 EA/PE) to afford the title compound as a yellow solid (9.7 g). ^1H NMR (400 MHz, CDCl_3): δ 10.35 (s, 1H), 7.77-7.74 (m, 1H), 6.92-6.87 (m, 1H), 3.97 (s, 3H).

Step 2: 5-Bromo-4-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

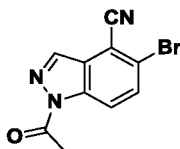
[00492] A mixture of 3-bromo-6-fluoro-2-methoxybenzaldehyde (9.7 g, 42 mmol), methoxyamine hydrochloride (3.65 g, 43.7 mmol), K_2CO_3 (6.61 g, 47.9 mmol), and DME (50 mL) was stirred at room temperature for 4 h under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated. The residue was dissolved in DME (20 mL), and hydrazine hydrate (20 mL) was added. The mixture was heated to 100 °C for 16 h. After cooling, EtOAc (100 mL) was added, and the reaction mixture separated into two layers. The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography on silica gel (1:5 EA/PE) to give 5-bromo-4-methoxy-1H-indazole as a brown solid (2.5 g). ^1H NMR (400 MHz, $DMSO-d_6$): δ 13.29 (s, 1H), 8.38 (s, 1H), 7.43 (d, 1H), 7.12 (d, 1H), 4.21 (s, 3H). Following General Procedure A, 5-bromo-4-methoxy-1H-indazole gave 5-bromo-4-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole: ^1H NMR (400 MHz, $DMSO-d_6$): δ 8.43 (s, 1H), 7.52 (d, 1H), 7.32 (d, 1H), 5.84-5.81 (m, 1H), 4.21 (s, 3H), 3.88-3.85 (m, 1H), 3.77-3.71 (m, 1H), 2.42-2.33 (m, 1H), 2.06-1.93 (m, 2H), 1.77-1.72 (m, 1H), 1.60-1.54 (m, 2H).

Intermediate 6**5-Bromo-1H-indazole-4-carbonitrile****Step 1: 3-Amino-2-methylbenzonitrile**

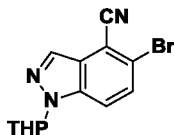
[00493] To a solution of 3-chloro-2-methylaniline (45 g, 0.32 mol) in NMP (100 mL), CuCN (56 g, 0.64 mol) was added. The mixture was stirred at 225 °C under N_2 for 8 hours. After cooled to ~50 °C, the reaction mixture was poured into concentrated ammonium hydroxide (500 mL), stirred at room temperature for one hour, and extracted with EtOAc (3x100 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (5:1 PE/EA) to afford the title compound (29 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.13-7.04 (m, 2H), 6.87 (dd, 1H), 3.82 (brs, 2H), 2.36 (s, 3H).

Step 2: 3-Amino-6-bromo-2-methylbenzonitrile

[00494] A 500 mL round bottom flask was charged with 3-amino-2-methylbenzonitrile (39 g, 0.30 mol), MeOH (800 mL) and AcOH (400 mL). Br₂ (47.3 g, 0.30 mol) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 15 minutes. The reaction mixture was diluted with aqueous Na₂S₂O₃ solution (74 g in 1.5L, 0.30 mol), stirred for 30 minutes, and then concentrated in vacuo. The residue was diluted with EtOAc (1 L), washed with saturated aqueous Na₂CO₃ (200 mL), washed with brine (200 mL), dried (Na₂SO₄), concentrated in vacuo and purified by column chromatography on silica gel (1:10 EA/PE) to afford the title compound as a yellow solid (43 g). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, 1H), 6.73 (d, 1H), 3.82 (brs, 2H), 2.38 (s, 3H).

Step 3: 1-Acetyl-5-bromo-1H-indazole-4-carbonitrile

[00495] A 500 mL three-necked round bottom flask, equipped with a thermometer and a mechanical stirrer, was charged with 3-amino-6-bromo-2-methylbenzonitrile (10.8 g, 51.2 mmol) and anhydrous toluene (150 mL). Acetic anhydride (17.1 g, 0.167 mol) was added dropwise under an atmosphere of N₂ while maintaining the internal temperature at 80-85 °C (an oil bath was used to initiate the reaction and was then removed). About 10 minutes after the addition (sm consumed by TLC), isoamyl nitrite (8.52 g, 72.8 mmol) was added dropwise at 80-90 °C under an atmosphere of N₂. The resulting mixture was heated at reflux for 45 minutes (caution: gas evolution). The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was washed with cold MeOH (-5 °C, 2x100 mL) and dried under vacuum to afford the title compound as a yellow solid (8.8 g).

Step 4: 5-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carbonitrile

[00496] Aqueous K₂CO₃ (3.39 g in 20 mL of water) was added dropwise (1 drop/3s) to a vigorously stirring mixture (at -30 °C) of 1-acetyl-5-bromo-1H-indazole-4-carbonitrile (8.8 g, 33 mmol) and MeOH (100 mL). The suspension slowly became clear. After 30 minutes, water (250 mL) was added slowly at -5 °C. The precipitate was collected by filtration, washed with water (2x200 mL), and dried under vacuum to give 5-bromo-1H-indazole-4-carbonitrile as a yellow solid (5.2 g). ¹H NMR (400 MHz, CDCl₃): δ 10.36 (brs, 1H), 8.24 (s, 1H), 7.64 (s, 2H); LCMS: 222

(M+H)⁺. Following General Procedure A, 5-bromo-1*H*-indazole-4-carbonitrile gave 5-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-4-carbonitrile: ¹H NMR (400 MHz, CDCl₃): δ 8.15 (s, 1H), 7.76 (d, 1H), 7.60 (d, 1H), 5.76 (dd, 1H), 3.98-3.94 (m, 1H), 3.77-3.71 (m, 1H), 2.52-2.44 (m, 1H), 2.17-2.09 (m, 2H), 1.80-1.69 (m, 3H).

Intermediate 7

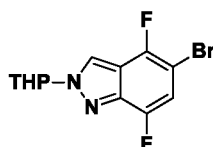
5-Bromo-3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-4-carbonitrile



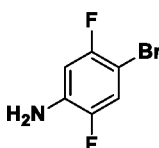
[00497] A 500 mL three-necked round bottom flask, equipped with a thermometer, was charged with 5-bromo-1*H*-indazole-4-carbonitrile (3.33 g, 15 mmol, Intermediate 6, Step 4a), CH₃CN (160 mL) and AcOH (40 mL). Selectfluor (10.62 g, 30 mmol) was added, and the resulting mixture was heated at 80 °C. After 1 day, more Selectfluor (5.31 g) was added. After 1 additional day, more Selectfluor (5.31 g) was added. After 1 additional day (3 days total), the reaction mixture was concentrated in vacuo, and the residue was poured into water (150 mL) and extracted with EtOAc (150 mL and 2x50 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (250 mL), washed with brine (3x200 mL), dried (Na₂SO₄), concentrated in vacuo, and purified by column chromatography on silica gel (1/10~1/3 EA/PE) to give 5-bromo-3-fluoro-1*H*-indazole-4-carbonitrile as a yellow solid (1.51 g). ¹H NMR (400 MHz, CDCl₃): δ 9.72 (brs, 1H), 7.61 (d, 1H), 7.46 (d, 1H); LCMS: 240 (M+H)⁺. Following General Procedure A, 5-bromo-3-fluoro-1*H*-indazole-4-carbonitrile gave 5-bromo-3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-4-carbonitrile: ¹H NMR (400 MHz, CDCl₃): δ 7.68-7.63 (m, 2H), 5.66-5.63 (m, 1H), 3.96-3.92 (m, 1H), 3.77-3.73 (m, 1H), 2.44-2.37 (m, 1H), 2.14-2.06 (m, 2H), 1.77-1.68 (m, 3H).

Intermediate 8

5-Bromo-4,7-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole

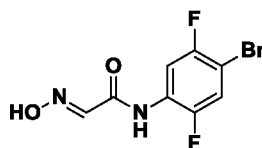


Step 1: 4-Bromo-2,5-difluoroaniline



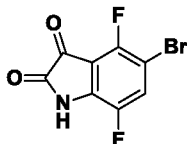
[00498] N-Bromosuccinimide (178 g, 1.0 mol) was added over 20 min to a solution of 2,5-difluoroaniline (129 g, 1.0 mol) in acetonitrile (1 L) at 0 °C. The resulting mixture was stirred at room temperature for 3 h, concentrated in vacuo, and poured into water (2 L). The mixture was extracted with ethyl acetate (2x500 mL), washed (200 mL brine), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was re-crystallized from PE (1 L) to afford the title compound as a gray solid (200 g). ¹H NMR (400 MHz, DMSO-d₆): δ 7.54-7.50 (m, 1H), 6.79-6.74 (m, 1H), 5.44 (s, 2H).

Step 2: N-(4-Bromo-2,5-difluorophenyl)-2-(hydroxyimino)acetamide



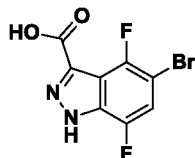
[00499] 4-Bromo-2,5-difluoroaniline (200 g, 0.96 mol), chloral hydrate (191 g, 1.16 mol) and hydroxylamine hydrochloride (135 g, 1.92 mol) were added to aqueous sulfuric acid (2%, 1225 mL). The resulting mixture was heated at 95 °C for 2 h, cooled to room temperature, and poured into ice water (5 L). The resulting precipitate was collected and dried to give the title compound (178 g, yield 66%). ¹H NMR (400 MHz, DMSO-d₆): δ 12.51 (s, 1H), 9.54 (s, 1H), 8.01-7.94 (m, 2H), 7.68 (s, 1H).

Step 3: 5-Bromo-4,7-difluoroindoline-2,3-dione



[00500] N-(4-Bromo-2,5-difluorophenyl)-2-(hydroxyimino)acetamide (178 g, 0.64 mol) was added to concentrated H₂SO₄ (500 mL) in a 2 L round bottom flask. The mixture was heated at 90 °C for 2 h, cooled to room temperature, and poured into ice water (5 L). The precipitate was collected by filtration to give ~200 g of crude product. A portion of the crude material (~100 g) was purified by column chromatography (PE/EA=2:1) to give the title compound (18 g). ¹H NMR (400 MHz, DMSO-d₆): δ 11.50 (s, 1H), 8.09 (dd, 1H).

Step 4: 5-Bromo-4,7-difluoro-1H-indazole-3-carboxylic acid



[00501] A solution of NaNO₂ (4.8 g, 68.7 mmol) in water (25 mL) at 0 °C was added to a solution of 5-bromo-4,7-difluoroindoline-2,3-dione (18 g, 68.7 mmol) and NaOH (3 g, 68.7 mmol) in water (30 mL) at 0 °C.

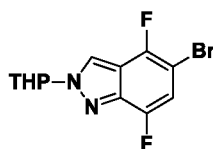
[00502] The mixture was kept at 0 °C for 20 min, slowly added to a solution of HBF₄ (14 mL, 0.14 mol) in water (20 mL) at 0 °C, and then stirred at 0 °C for 30 min. The reaction mixture was slowly added to a mixture of SnCl₂·2H₂O (39 g, 0.17 mol) and concentrated HCl (65 mL), and then stirred at room temperature overnight. The precipitate was collected by filtration and dried to afford the title compound (13 g, purity 70-80%), which was used directly in the following step without further purification. ¹H NMR (400 MHz, DMSO-d₆): δ 14.55 (brs, 1H), 12.35 (brs, 1H), 8.01-7.87 (m, 1H).

Step 5: 5-Bromo-4,7-difluoro-1H-indazole



[00503] A mixture of 5-bromo-4,7-difluoro-1H-indazole-3-carboxylic acid (13 g, 47 mmol) in diphenyl ether (200 mL) was heated at 205 °C for 4 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by column chromatography (PE/EA=10:1) to afford the title compound as a yellow solid (2 g). ¹H NMR (400 MHz, DMSO-d₆): δ 13.94 (brs, 1H), 8.42 (d, 1H), 7.89 (dd, 1H).

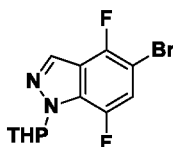
Step 6: 5-Bromo-4,7-difluoro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole



[00504] To a mixture of 5-bromo-4,7-difluoro-1H-indazole (1.9 g, 8.2 mmol), *p*-toluenesulfonic acid (154 mg, 0.81 mmol), and DCM (20 mL), DHP (2.7 g, 33 mmol) was added under N₂ atmosphere at room temperature. The resulting mixture was stirred at room temperature for 18 h and diluted with DCM (300 mL). The organic layer was washed (200 mL, H₂O), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE:EA=20:1~5:1) to afford 5-bromo-4,7-difluoro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole (1.4 g). ¹H NMR (400 MHz, DMSO-d₆): δ 8.44 (s, 1H), 7.97 (dd, 1H), 6.34 (dd, 1H), 3.92-3.89 (m, 1H), 3.77-3.71 (m, 1H), 2.47-2.40 (m, 1H), 2.10-2.03 (m, 2H), 1.75-1.67 (m, 1H), 1.59-1.53 (m, 2H).

Intermediate 9

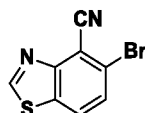
5-Bromo-4,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



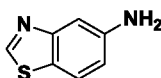
[00505] The title compound was isolated during the purification of Intermediate 8, Step 6. ¹H NMR (400 MHz, CDCl₃): δ 8.14 (s, 1H), 7.49 (dd, 1H), 6.42 (dd, 1H), 4.05-4.01 (m, 1H), 3.84-3.77 (m, 1H), 2.66-2.62 (m, 1H), 2.20-2.12 (m, 2H), 1.79-1.70 (m, 2H), 1.67-1.58 (m, 1H).

Intermediate 10

5-Bromobenzo[d]thiazole-4-carbonitrile

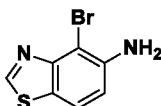


Step 1: Benzo[d]thiazol-5-amine



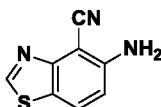
[00506] A mixture of 5-nitrobenzo[d]thiazole (3.0 g, 16.7 mmol) and SnCl₂·2H₂O (19 g, 84.2 mmol) in EtOAc (150 mL) was stirred at reflux overnight. The reaction mixture was basified with Et₃N until pH ~8 and the precipitate was filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc/DCM = 2:1) to afford the title compound as a yellow solids (2.1 g). ¹H NMR (400 MHz, CDCl₃): δ 8.92 (s, 1H), 7.69 (d, 1H), 7.41 (d, 1H), 6.86 (dd, 1H), 3.82 (brs, 2H); LCMS: 151 (M+H)⁺.

Step 2: 4-Bromobenzo[d]thiazol-5-amine



[00507] A solution of Br₂ (2.3 g, 14.4 mmol) in CHCl₃ (10 mL) was added dropwise to a solution of benzo[d]thiazol-5-amine (2.1 g, 14.0 mmol) in CHCl₃ (100 mL) at 10 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was basified with saturated aqueous Na₂CO₃ (100 mL) and extracted with DCM (3x30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1:8~1:4) to afford the title compound as yellow solids (2.3 g). ¹H NMR (300 MHz, CDCl₃): δ 9.01 (s, 1H), 7.66 (d, 1H), 6.95 (d, 1H), 4.33 (s, 2H).

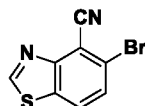
Step 3: 5-Aminobenzo[d]thiazole-4-carbonitrile



[00508] A microwave reaction tube was charged with 4-bromobenzo[d]thiazol-5-amine (500 mg, 2.2 mmol), CuCN (260 mg, 2.9 mmol) and NMP (10 mL). Nitrogen was bubbled into the reaction solution for 10 minutes, and the mixture was heated at 170 °C for 1.5 h in a microwave reactor. The reaction mixture was diluted with concentrated ammonium hydroxide (50 mL), stirred

at room temperature for 1 h, and filtered through celite. The filtrate was extracted with EtOAc (4x20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and then concentrated in vacuo. The residue was further purified by column chromatography on silica gel with 35% EtOAc in petroleum ether to afford the title compound as yellow solids (190 mg.). ¹H NMR (400 MHz, CDCl₃): δ 9.07 (s, 1H), 7.84 (d, 1H), 6.88 (d, 1H), 4.69 (s, 2H).

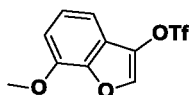
Step 4: 5-Bromobenzo[d]thiazole-4-carbonitrile



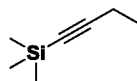
[00509] A solution of NaNO₂ (350 mg, 5.38 mmol) in water (1.0 mL) was added dropwise to a solution of 5-aminobenzo[d]thiazole-4-carbonitrile (1.0 g, 5.70 mmol) in aqueous HBr (40%, 10 mL) in an ice bath. After being stirred at 0 °C for 1 hour, the mixture was added dropwise to a solution of CuBr (980 mg, 6.85 mmol) in aqueous HBr (40%, 10 mL) at 10 °C. The resulting mixture was stirred at room temperature for 1 h. Work-up: the reaction mixture was basified with conc. ammonia (50 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and then concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel with 20% EtOAc in petroleum ether to afford the title compound as yellow solids (800 mg). ¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, 1H), 8.05 (d, 1H), 7.74 (d, 1H).

Intermediate 11

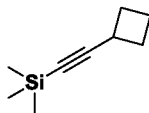
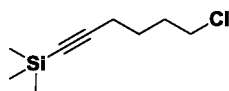
7-Methoxybenzofuran-3-yl trifluoromethanesulfonate



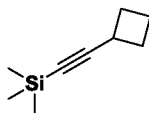
[00510] Trifluoromethanesulfonic anhydride (4.6 g, 16.3 mmol) was added dropwise to a solution of 7-methoxybenzofuran-3(2H)-one (1.8 g, 10.9 mmol), triethylamine (2.2 g, 21.8 mmol), and dichloromethane (40 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 2 h. The reaction mixture was neutralized with saturated aqueous NaHCO₃ (22 mL). The organic layer was separated, washed with water (40 mL) and brine (40 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified on a silica gel column using petroleum ether to afford the title compound as yellow oil (2.3 g, yield 71%). ¹H NMR (DMSO-d₆, 400 MHz): δ 8.67 (s, 1H), 7.36 (t, 1H), 7.21 (d, 1H), 7.20 (d, 1H), 3.96 (s, 3H).

Intermediate 12**But-1-yn-1-yltrimethylsilane**

[00511] A 3 L three-necked round bottom flask was charged with (trimethylsilyl)acetylene (116 g, 1.19 mol) and dry THF (400 mL). The solution was cooled to -78 °C. To this solution, butyllithium in hexane (2.5 M, 500 mL, 1.25 mol) was added dropwise over 2 hours. The resulting mixture was warmed to 0 °C for 10 minutes and then re-cooled to -78 °C. HMPA (234 g, 1.31 mol) was added, and the mixture was stirred at -78 °C for 30 minutes. To this solution, iodoethane (200 g, 1.28 mol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction mixture was washed with water (4x600 mL) and then brine (2x500 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Hexane and THF were distilled off at 75~110 °C. But-1-yn-1-yltrimethylsilane was distilled between 125 to 135 °C affording 91 g of a colorless liquid (61%). ¹H NMR (400 MHz, DMSO-d₆) δ 2.20 (q, 2H), 1.05 (t, 3H), 0.11 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 108.8, 83.3, 13.7, 13.4, 0.0.

Intermediate 13**(Cyclobutylethynyl)trimethylsilane****Step 1: (6-Chlorohex-1-yn-1-yl)trimethylsilane**

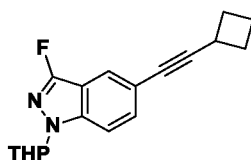
[00512] To a solution of 6-chlorohex-1-yne (100 mL, 94.6 g, 0.82 mol) in anhydrous Et₂O (500 mL) at -78 °C, n-butyllithium (2.5 M in hexane, 360 mL, 0.90 mol) was added over 40 minutes. The resulting mixture was stirred for 30 minutes at -78 °C. Chlorotrimethylsilane (125 mL, 1.0 mol) was then added. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was carefully quenched with saturated aqueous NH₄Cl (300 mL) at room temperature and extracted with Et₂O (2x200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo to afford the title compound (144 g, yield 93%). ¹H NMR (DMSO-d₆, 400 MHz): δ 3.65 (t, 2H), 2.25 (t, 2H), 1.82-1.75 (m, 2H), 1.58-1.51 (m, 2H), 0.12 (s, 9H).

Step 2: (Cyclobutylethynyl)trimethylsilane

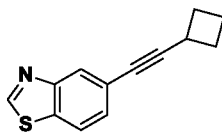
[00513] To a solution of diisopropylamine (153 g, 1.52 mol) in anhydrous THF (1.0 L) at 0 °C, n-butyllithium (2.5 M in hexane, 608 mL, 1.52 mol) was added dropwise. The mixture was stirred for 20 minutes at 0 °C and then cooled to -78 °C. To this mixture, a solution of (6-chlorohex-1-yn-1-yl)trimethylsilane (144 g, 0.76 mol) in anhydrous THF (200 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was carefully quenched at room temperature with saturated aqueous NH₄Cl (500 mL), and then extracted with pentane (2x200 mL). The combined organic layers were washed with brine (500 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated on a rotary evaporator. The residue was distilled at 160-162 °C/760 Torr to afford the title compound as a colorless liquid (81 g, yield 70 %). ¹H NMR (CDCl₃, 400 MHz): δ 3.05-3.01 (m, 1H), 2.26-2.20 (m, 2H), 2.17-2.10 (m, 2H), 1.93-1.84 (m, 2H), 0.11 (s, 9H).

Intermediate 14

5-(Cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



[00514] Nitrogen was bubbled through a solution of 5-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (11 g, 36.8 mmol, Intermediate 1) and DMA (40 mL) for 5 min. With continued N₂ bubbling, CuI (699 mg, 3.68 mmol), Pd(OAc)₂ (826 mg, 3.68 mmol), dppf (2.04 g, 3.68 mmol), Cs₂CO₃ (16.8 g, 51.5 mmol), and (cyclobutylethynyl)trimethylsilane (7.3 g, 47.8 mmol, Intermediate 13) were added in sequence. The reaction mixture was heated at 80 °C under N₂ for 10 h, diluted with ethyl acetate (400 mL) and water (200 mL), and then filtered. The aqueous layer was extracted with ethyl acetate (50 mL × 2), and the organic extracts were combined with organic layer of the filtrate. The combined organics were washed with brine (100 mL × 3), dried (Na₂SO₄), filtered, concentrated, and purified by silica gel chromatography (1:70; ethyl acetate:petroleum ether) to give 7.4 g of 5-(cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole as a yellow solid. ¹H NMR (400 MHz; DMSO-d₆): δ 7.77 (s, 1H), 7.73 (d, 1H), 7.49 (dd, 1H), 5.80-5.78 (m, 1H), 3.88-3.86 (m, 1H), 3.75-3.68 (m, 1H), 3.31-3.25 (m, 1H), 2.35-2.27 (m, 2H), 2.24-2.10 (m, 3H), 2.01-1.85 (m, 4H), 1.74-1.65 (m, 1H), 1.57-1.51 (m, 2H); LCMS: 299 (M+H)⁺.

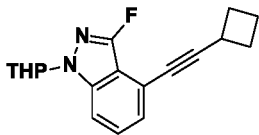
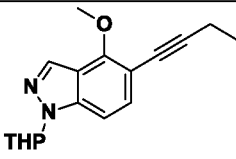
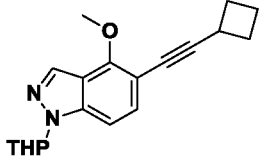
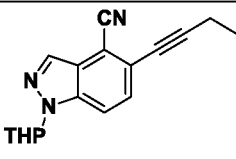
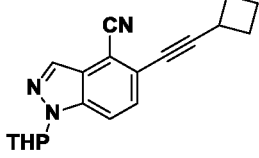
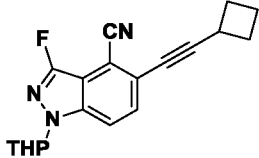
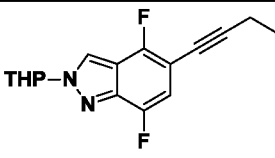
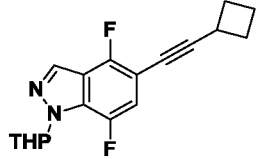
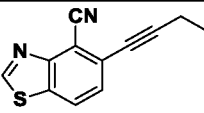
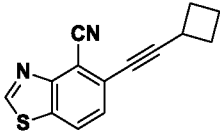
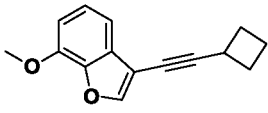
Intermediate 15**5-(Cyclobutylethynyl)benzo[d]thiazole**

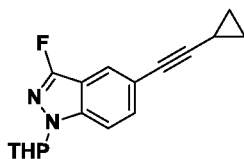
[00515] A mixture of 5-bromobenzo[d]thiazole (5 g, 23.4 mmol), (cyclobutylethynyl)trimethylsilane (5.3 g, 35.1 mmol, Intermediate 13), Pd(OAc)₂ (261 mg, 1.2 mmol), dppf (647 mg, 1.2 mmol), CuI (222 mg, 1.2 mmol), cesium carbonate (11.4 g, 35.1 mmol), and DMA (60 mL) was heated at 90 °C under N₂ for 90 min and then cooled to room temperature. The reaction mixture was diluted with EtOAc and H₂O and filtered through celite. The organic layer of the filtrate was separated, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified on silica gel column to afford 4 g of 5-(cyclobutylethynyl)benzo[d]thiazole as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.42 (s, 1H), 8.14 (d, 1H), 8.06 (s, 1H), 7.46 (dd, 1H), 3.31 (m, 1H), 2.36-2.28 (m, 2H), 2.21-2.11 (m, 2H), 1.99-1.86 (m, 2H); LCMS: 214 (M+H)⁺.

[00516] The Intermediates in Table 3 were prepared from the heteroaryl-bromide Intermediates described herein following the procedures outlined for Intermediates 14 & 15 or in General Procedure B.

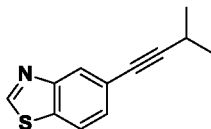
Table 3.

Intermediate 16	5-(But-1-yn-1-yl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 17	5-(Cyclobutylethynyl)-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 18	5-(But-1-yn-1-yl)-3,4-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 19	4-(But-1-yn-1-yl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	

Intermediate 20	4-(Cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 21	5-(But-1-yn-1-yl)-4-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 22	5-(Cyclobutylethynyl)-4-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 23	5-(But-1-yn-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carbonitrile	
Intermediate 24	5-(cyclobutylethynyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carbonitrile	
Intermediate 25	5-(Cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carbonitrile	
Intermediate 26	5-(But-1-yn-1-yl)-4,7-difluoro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole	
Intermediate 27	5-(Cyclobutylethynyl)-4,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	
Intermediate 28	5-(But-1-yn-1-yl)benzo[d]thiazole-4-carbonitrile	
Intermediate 29	5-(Cyclobutylethynyl)benzo[d]thiazole-4-carbonitrile	
Intermediate 30	3-(Cyclobutylethynyl)-7-methoxybenzofuran	

Intermediate 31**5-(Cyclopropylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole**

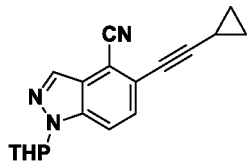
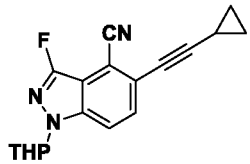
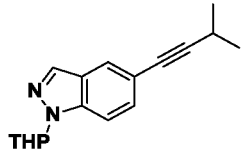
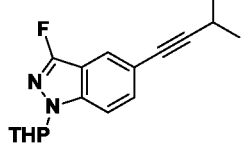
[00517] A mixture of 5-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (3.86 g, 12.9 mmol, Intermediate 1), Pd(PPh₃)₂Cl₂ (0.91 g, 1.3 mmol), CuI (0.25 g, 1.3 mmol), and triethylamine (65 mL) was degassed with three vacuum/N₂ cycles. Ethynylcyclopropane (2.56 g, 38.7 mmol) was added, and the reaction mixture was stirred at 80 °C under N₂ for 8 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed (2x100 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified on a silica gel column to give the title compound (3.53 g) as a brown oil. ¹H NMR (400 MHz, DMSO-d₆): δ 7.72 (s, 1H), 7.65 (dd, 1H), 7.46 (dd, 1H), 5.78 (m, 1H), 3.89-3.82 (m, 1H), 3.73-3.67 (m, 1H), 2.37-2.18 (m, 1H), 2.03-1.90 (m, 2H), 1.78-1.65 (m, 1H), 1.60-1.50 (m, 3H), 0.90-0.85 (m, 2H), 0.68-0.70 (m, 2H); LCMS: 201 [(M-THP+H)+H]⁺.

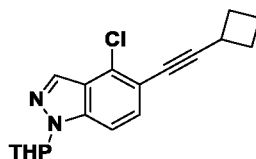
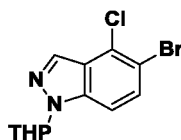
Intermediate 32**5-(3-Methylbut-1-yn-1-yl)benzo[d]thiazole**

[00518] A mixture of 5-bromobenzothiazole (1 g, 4.7 mmol), 3-methylbut-1-yne (2.9 mL, 28.0 mmol), and CuI (177 mg, 0.9 mmol) in triethylamine (9 mL) was placed in a sealed tube followed by addition of PdCl₂(PPh₃)₂ (327 mg, 0.5 mmol). The resulting mixture was heated to 90 °C overnight and then cooled to room temperature. The reaction mixture was diluted with EtOAc and H₂O and filtered through celite. The organic layer of the filtrate was separated, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified on silica gel column to afford 750 mg of 5-(cyclobutylethynyl)benzo[d]thiazole as a brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.42 (s, 1H), 8.13 (d, 1H), 8.04 (s, 1H), 7.45 (dd, 1H), 2.84 (m, 1H), 1.24 (d, 6H); LCMS: 202 (M+H)⁺.

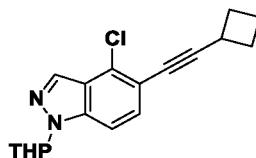
[00519] The Intermediates in Table 4 were prepared from the heteroaryl-bromide Intermediates described herein following the procedures outlined for Intermediates 31 & 32.

Table 4.

Intermediate 33	5-(Cyclopropylethynyl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole-4-carbonitrile	
Intermediate 34	5-(Cyclopropylethynyl)-3-fluoro-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole-4-carbonitrile	
Intermediate 35	5-(3-Methylbut-1-yn-1-yl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	
Intermediate 36	3-Fluoro-5-(3-methylbut-1-yn-1-yl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	

Intermediate 37**4-Chloro-5-(cyclobutylethynyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole****Step 1: 5-Bromo-4-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole**

[00520] The title compound was prepared from 5-bromo-4-chloro-1*H*-indazole following General Procedure A. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.20 (s, 1H), 7.75-7.69 (m, 2H), 5.89 (dd, 1H), 3.90-3.84 (m, 1H), 3.79-3.69 (m, 1H), 2.42-2.32 (m, 1H), 2.07-1.95 (m, 2H), 1.80-1.66 (m, 1H), 1.62-1.54 (m, 2H).

Step 2: 4-Chloro-5-(cyclobutylethynyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

[00521] A solution of tetrabutylammonium fluoride (6 mL; 1M solution in THF) and THF (6 mL) was degassed with three vacuum/N₂ cycles. (Cyclobutylethynyl)trimethylsilane (972 mg, 6.38 mmol, Intermediate 13) was added, and the mixture was stirred at rt for 10 min. This solution was

added to a mixture of 5-bromo-4-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (1.00 g, 3.18 mmol), Pd(PPh₃)₄ (736 mg, 0.64 mmol), and CuI (243 mg, 1.28 mmol), and then degassed with three vacuum/N₂ cycles. The reaction was heated at 80 °C for 19 h, allowed to cool to rt, and then diluted with EtOAc (~100 mL). The EtOAc was washed with water (2 x 75 mL), washed with brine (75 mL), dried (MgSO₄), filtered, concentrated and purified by silica gel chromatography (0% - 10% EtOAc in hexanes) to give the title compound as a tan solid (929 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 8.18 (s, 1H), 7.71 (d, 1H), 7.48 (d, 1H), 5.87 (d, 1H), 3.91-3.82 (m, 1H), 3.80-3.69 (m, 1H), 3.39-3.32 (m, 1H), 2.45-2.29 (m, 3H), 2.25-2.10 (m, 2H), 2.08-1.88 (m, 4H), 1.81-1.68 (m, 1H), 1.63-1.54 (m, 2H). LCMS: 231 [(M-THP+H)+H]⁺.

Intermediate 38

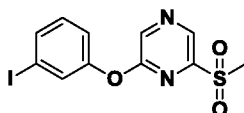
3-Iodo-4-methylthiophene



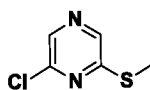
[00522] A mixture of 3-bromo-4-methylthiophene (25g, 141 mmol), NaI (46.6 g, 310 mmol), copper iodide, (2.68 g, 14 mmol), and *N,N'*-dimethylethane-1,2-diamine (3 mL, 28 mmol) in *n*-BuOH (200 mL) was heated to 130 °C for 40h. The reaction was monitored by NMR. The mixture was cooled and poured into NH₄OH, then extracted with hexanes (3x). The organic phases were combined, dried, and evaporated (water bath was kept below 35°C to prevent loss of product) in order to remove all of the hexanes and half of the *n*-BuOH. The residue (still containing half of the *n*-BuOH) was purified by column chromatography (100% hexanes) to afford a solution of the desired in *n*-BuOH (amount of *n*-BuOH significantly reduced). This solution was chromatographed again through silica to afford 25 g of 3-iodo-4-methylthiophene as a colorless oil. ¹H NMR (400 MHz, DMSO-d₆): δ 7.72 (s, 1H), 7.27 (s, 1H), 2.15 (s, 3H).

Intermediate 39

2-(3-Iodophenoxy)-6-(methylsulfonyl)pyrazine



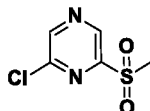
Step 1: 2-Chloro-6-(methylthio)pyrazine



[00523] Methyl mercaptan sodium salt (4.4 mL, 9.4 mmol, 15% in H₂O) was added to a mixture of 2,6-dichloropyrazine (1.57g, 10.5 mmol), K₂CO₃ (1.32g, 9.5 mmol), and anhydrous DMF (24 mL) at rt. The reaction was stirred for 19.5 h, diluted with H₂O (50 mL), and then extracted with

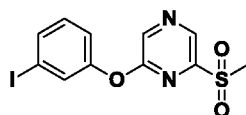
EtOAc (2x50 mL). The organic extracts were combined, washed with H₂O (50 mL), washed with sat. Na₂SO₃ (50 mL), washed with brine (50 mL), dried (MgSO₄), filtered, concentrated and purified by silica gel chromatography (0%-5% EtOAc in hexanes) to give 2-chloro-6-(methylthio)pyrazine as a clear liquid (1.2 g). ¹H NMR (400 MHz, DMSO-d₆): δ 8.62 (s, 1H), 8.45 (s, 1H), 2.57 (s, 3H). LCMS: 161 (M+H)⁺.

Step 2: 2-Chloro-6-(methylsulfonyl)pyrazine



[00524] A solution of 2-chloro-6-(methylthio)pyrazine (1.2 g, 7.6 mmol) and DCM (60 mL) was added to a solution of mCPBA (3.9 g, 17.5 mmol, 77%) and DCM (415 mL) at -3 °C (internal temperature maintained ≤ -1 °C). The reaction was allowed to warm to 0 °C, and the ice bath was removed. The reaction was stirred at rt for ~2 additional hours, washed with NaHCO₃ (400 mL), washed with brine (400 mL), dried (MgSO₄), filtered and concentrated. The crude material was dissolved in DCM, washed with NaHCO₃ (3x75 mL), washed with brine (75 mL), dried (MgSO₄), filtered and concentrated to give crude 2-chloro-6-(methylsulfonyl)pyrazine as a white solid (1.2 g). ¹H NMR (400MHz, DMSO-d₆): δ 9.23 (s, 1H), 9.21 (s, 1H), 3.39 (s, 3H). LCMS: 193 (M+H)⁺.

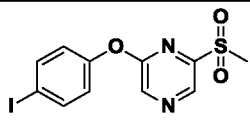
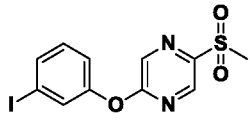
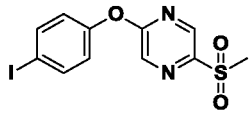
Step 3: 2-(3-Iodophenoxy)-6-(methylsulfonyl)pyrazine

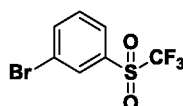


[00525] A mixture of 2-chloro-6-(methylsulfonyl)pyrazine (569 mg, 2.95 mmol), K₂CO₃ (818 mg, 5.92 mmol), 3-iodophenol (789 mg, 3.58 mmol), and DMF (7.4 mL) was heated at 90 °C for 3 h and then allowed to cool to rt. The reaction was diluted with EtOAc, washed with H₂O (2x50 mL), washed with brine (50 mL), dried (MgSO₄), filtered, concentrated and purified by silica gel chromatography (10%-30% EtOAc in hexanes) to give 2-(3-iodophenoxy)-6-(methylsulfonyl)pyrazine as a white solid (465 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 8.93 (s, 1H), 8.92 (s, 1H), 7.80-7.79 (m, 1H), 7.71-7.68 (m, 1H), 7.40-7.37 (m, 1H), 7.32-7.27 (m, 1H), 3.19 (s, 3H). LCMS: 377 (M+H)⁺.

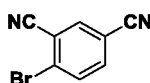
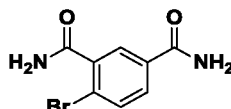
[00526] The Intermediates in Table 5 were prepared from 2-chloro-6-(methylsulfonyl)pyrazine or 2-bromo-5-(methylsulfonyl)pyrazine and the appropriate iodophenol following the procedure outlined for Intermediate 39, Step 3.

Table 5.

Intermediate 40	2-(4-Iodophenoxy)-6-(methylsulfonyl)pyrazine	
Intermediate 41	2-(3-Iodophenoxy)-5-(methylsulfonyl)pyrazine	
Intermediate 42	2-(4-Iodophenoxy)-5-(methylsulfonyl)pyrazine	

Intermediate 43**1-Bromo-3-((trifluoromethyl)sulfonyl)benzene**

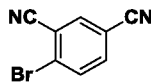
[00527] Chromium(VI) oxide (1.56 g, 15.6 mmol) was added to a mixture of (3-bromophenyl)(trifluoromethyl)sulfane (1.56 g, 6.1 mmol), H₂O (13 mL), and H₂SO₄ (8 mL). The resulting mixture was stirred at rt for 16 hours, poured into ice-water (200 mL), and extracted with EtOAc (3x50 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (50 mL), washed with brine (50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by prep-HPLC to afford the title compound (310 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 8.31-8.27 (m, 2H), 8.18 (d, 1H), 7.82 (t, 1H).

Intermediate 44**4-Bromoisophthalonitrile****Step 1: 4-Bromoisophthalamide**

[00528] Thionyl chloride (5 mL) and 1 drop of DMF were added to 4-bromoisophthalic acid (1.22 g, 5.0 mmol). The white suspension was heated at 65 °C for 4 hrs and allowed to cool to rt. The mixture was azeotroped twice with toluene and dried under high vacuum. A solution of the residue in dioxane (3 mL) was added to a solution of ammonium hydroxide (2 mL) in dioxane (5 mL). [Caution: Exotherm! Internal temperature rose to 63 °C]. The resulting mixture was stirred at rt (until complete by LCMS), cooled to 10 °C, diluted with water (20 mL), and filtered. The filter cake

was dried under high vacuum to give 4-bromoisophthalamide as a white solid (874 mg). ^1H NMR (400MHz, DMSO- d_6): δ 8.09 (bs, 1H), 7.93 (bs, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 1H), 7.64 (bs, 1H), 7.50 (bs, 1H); LCMS: 243 (M+H) $^+$.

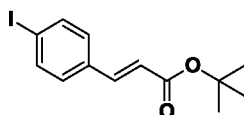
Step 2: 4-Bromoisophthalonitrile



[00529] Phosphorus oxychloride (4 mL) and 1 drop of DMF were added to 4-bromoisophthalamide (868 mg, 3.6 mmol). The reaction was heated at 90 °C for 1.5 hrs, allowed to cool to rt, pipetted onto ice, and then stirred for 10 min. The solids were filtered, rinsed with water, and dried under high vacuum to give the title compound as a white solid (671 mg). ^1H NMR (400MHz, DMSO- d_6): δ 8.59-8.56 (m, 1H), 8.15-8.08 (m, 2H).

Intermediate 45

(E)-*tert*-Butyl 3-(4-iodophenyl)acrylate

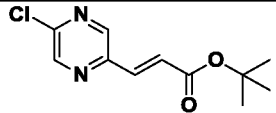
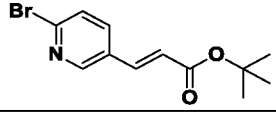
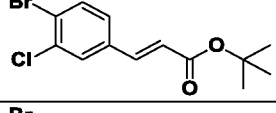
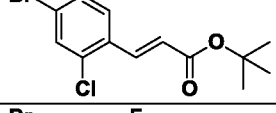
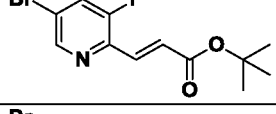
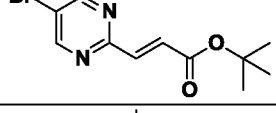
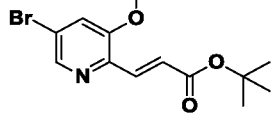
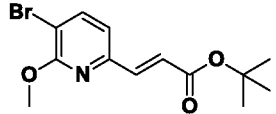
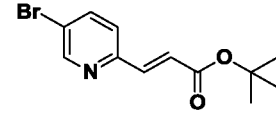
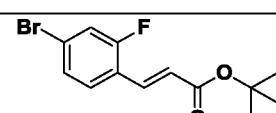
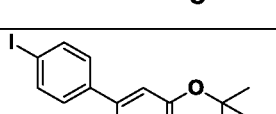
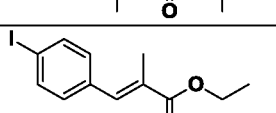


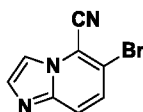
[00530] A solution of DBU (7.1 mL, 47.4 mmol) and anhydrous acetonitrile (14 mL) was slowly added dropwise via addition funnel to a mixture of 4-iodobenzaldehyde (10.0 g, 43.1 mmol), *tert*-butyl diethylphosphonoacetate (12.1 mL, 51.7 mmol), lithium chloride (3.7 g, 86.2 mmol) and anhydrous acetonitrile (86 mL). After stirring at room temperature for 1.5 h, the reaction was concentrated and then redissolved in DCM and water. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified on a silica gel column eluted with 0-5% ethyl acetate in hexanes affording the title compound as pale yellow foam (13.2 g). ^1H NMR (400 MHz, DMSO- d_6): δ 7.76 (d, 2H), 7.50-7.46 (m, 3H), 6.54 (d, 1H), 1.47 (s, 9H).

[00531] The Intermediates in Table 6 were prepared from commercially available aldehydes or ketones following the procedure outlined for Intermediate 45 or in General Procedure E.

Table 6.

Intermediate 46	(E)- <i>tert</i> -Butyl 3-(5-bromo-6-methylpyridin-2-yl)acrylate	
Intermediate 47	(E)- <i>tert</i> -Butyl 3-(5-bromo-3-methylpyridin-2-yl)acrylate	

Intermediate 48	(E)- <i>tert</i> -Butyl 3-(5-chloropyrazin-2-yl)acrylate	
Intermediate 49	(E)- <i>tert</i> -Butyl 3-(6-bromopyridin-3-yl)acrylate	
Intermediate 50	(E)- <i>tert</i> -Butyl 3-(4-bromo-3-chlorophenyl)acrylate	
Intermediate 51	(E)- <i>tert</i> -Butyl 3-(4-bromo-2-chlorophenyl)acrylate	
Intermediate 52	(E)- <i>tert</i> -Butyl 3-(5-bromo-3-fluoropyridin-2-yl)acrylate	
Intermediate 53	(E)- <i>tert</i> -Butyl 3-(5-bromopyrimidin-2-yl)acrylate	
Intermediate 54	(E)- <i>tert</i> -Butyl 3-(5-bromo-3-methoxypyridin-2-yl)acrylate	
Intermediate 55	(E)- <i>tert</i> -Butyl 3-(5-bromo-6-methoxypyridin-2-yl)acrylate	
Intermediate 59	(E)- <i>tert</i> -Butyl 3-(5-bromopyridin-2-yl)acrylate	
Intermediate 60	(E)- <i>tert</i> -Butyl 3-(4-bromo-2-fluorophenyl)acrylate	
Intermediate 61	(E)- <i>tert</i> -Butyl 3-(4-iodophenyl)but-2-enoate	
Intermediate 62	(E)-Ethyl 3-(4-iodophenyl)-2-methylacrylate	

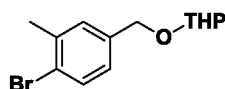
Intermediate 63**6-Bromoimidazo[1,2-a]pyridine-5-carbonitrile**

2-Chloroacetaldehyde (50% wt in water; 0.20 mL, 1.6 mmol) was added to a suspension of 6-amino-3-bromo-2-cyanopyridine (111 mg, 0.561 mmol) in ethanol (1 mL). The reaction was heated at

reflux for 5 h, allowed to cool to rt and then concentrated. The residue was diluted with ethyl acetate, water and then 5M NaOH. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 40 mL). The ethyl acetate extracts were combined, washed with water (50 mL), dried (MgSO_4), filtered and concentrated. The residue was purified by silica gel chromatography (20%-60% ethyl acetate in hexanes) to give 86 mg of 6-bromoimidazo[1,2-a]pyridine-5-carbonitrile as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.95 (d, 1H), 7.85 (dd, 1H), 7.33 (d, 1H); LCMS: 222 ($\text{M}+\text{H}$) $^+$.

Intermediate 64

2-((4-Bromo-3-methylbenzyl)oxy)tetrahydro-2H-pyran



A mixture of (4-bromo-3-methylphenyl)methanol (774 mg, 3.85 mmol), 3,4-dihydro-2H-pyran (0.69 mL, 7.7 mmol), and pyridinium p-toluenesulfonate (290 mg, 1.15 mmol) in dichloromethane (7 mL) was stirred at room temperature for 4 h. The reaction mixture was absorbed on silica gel and purified by flash chromatography eluting with 0 to 50% ethyl acetate/hexanes to afford 1 g of 2-((4-bromo-3-methylbenzyl)oxy)tetrahydro-2H-pyran as a clear oil. ^1H NMR (400 MHz; DMSO-d_6): δ 7.53 (d, 1H), 7.31 (s, 1H), 7.10 (dd, 1H), 4.65 (m, 1H), 4.60 (d, 1H), 4.38 (d, 1H), 3.76 (m, 1H), 3.45 (m, 1H), 2.34 (s, 3H), 1.98-1.45 (m, 6H).

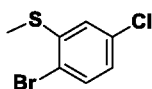
The Intermediate in Table 7 was prepared from (4-bromo-3-chlorophenyl)methanol following the procedure outlined for Intermediate 64.

Table 7.

Intermediate 65	2-((4-Bromo-3-chlorobenzyl)oxy)tetrahydro-2H-pyran	
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Intermediate 66

(2-Bromo-5-chlorophenyl)(methyl)sulfane



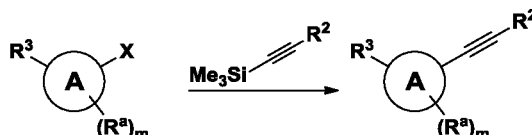
To a solution of 2-bromo-5-chloroaniline (1.53 g, 7.40 mmol) and 1,2-dimethyldisulfane (0.63 mL, 7.00 mmol) in acetonitrile (17 mL) at 60 °C was added *tert*-butyl nitrite (1.1 mL, 8.1 mmol). The mixture was heated at 60 °C for 3 h, cooled to room temperature and concentrated under reduced pressure. The crude material was purified on a silica gel column to yield the desired compound

(1.25 g, 71%) as a beige solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.59 (d, 1H), 7.24 (d, 1H), 7.13 (dd, 1H), 2.52 (s, 3H).

General Procedure A: Installation of a protecting group for the OH or NH of halo-heterocycles.

[00532] The most common protecting group was THP, especially for indazoles: 3,4-Dihydro-2H-pyran (1.02-10 equiv) was added to a solution of the appropriate halo-heterocycle (1.0 equiv), PPTS (or pTsOH, 0.05-0.3 equiv), and dichloromethane (~2 mL/mmol) at room temperature. The reaction was stirred under N_2 for 6-48 h (until complete by TLC or LCMS), quenched with water, and then extracted with dichloromethane. The extracts were dried, filtered, concentrated, and purified by silica gel chromatography to give the protected halo-heterocycle. In cases where THP is not a suitable protecting group, BOC or Trityl were commonly installed. BOC: di-tert-butyl dicarbonate (1.1-2.0 equiv) was added to a solution of the appropriate halo-heterocycle (1.0 equiv), DMAP (0.01-0.2 equiv), and dichloromethane. The reaction was stirred at room temperature until complete by TLC or LCMS. The reaction was concentrated and purified by silica gel chromatography to give the protected halo-heterocycle. Trityl: Trityl chloride (1.05-1.5 equiv) was added to a solution of the appropriate halo-heterocycle (1.0 equiv), triethylamine (or other suitable base, 1.1-2.0 equiv), and dichloromethane. The reaction was stirred at room temperature until complete by TLC or LCMS. The reaction was diluted with dichloromethane, washed with water, dried, filtered, concentrated, and purified by silica gel chromatography to give the protected halo-heterocycle. Other protecting groups less commonly used include acetyl, MOM, SEM.

General Procedure B: Coupling of the halo-heterocycles with alkynyl-trimethylsilanes.



[00533] A mixture of the appropriate halo-heterocycle (1.0 equiv), Cs_2CO_3 (1.2-3.0 equiv), CuI (0.05-0.2 equiv), $\text{Pd}(\text{OAc})_2$ (0.05-0.2 equiv), dppf (0.05-0.2 equiv), and *N,N*-dimethylacetamide (DMA, 1-2 mL/mmol) was degassed with three vacuum/nitrogen cycles. The appropriate alkynyl-trimethylsilane (1.3-2.0 equiv) was added, and the reaction was heated at 80 °C under N_2 for 1-24 hours (until complete by TLC or LCMS). The reaction was allowed to cool to room temperature, diluted with ethyl acetate (or diethyl ether) and water, and then filtered through Celite. The aqueous layer was separated and extracted with ethyl acetate (or diethyl ether). The organics were combined, dried, filtered, concentrated, and then purified by silica gel column chromatography to give the alkynyl-heterocycle.

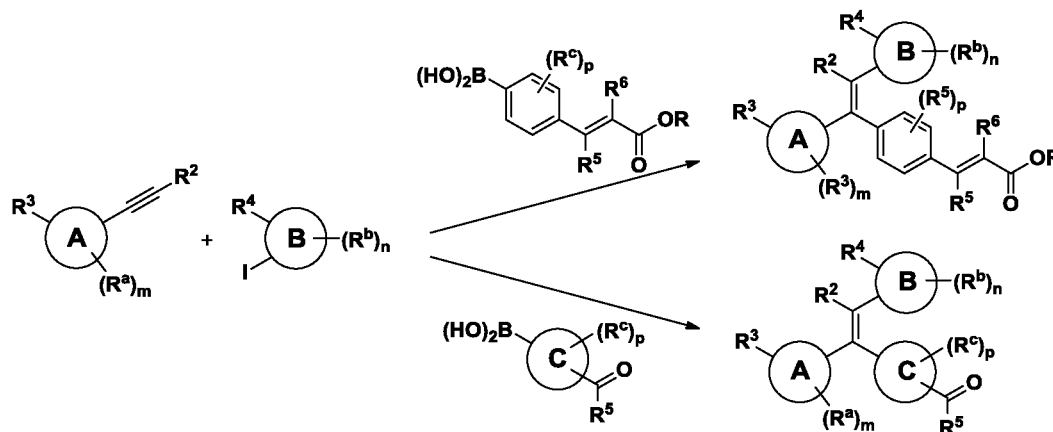
[00534] Note: Alternate bases utilized include K_2CO_3 and CsF; Alternate ligands utilized include 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride and Ph_3P ; Alternate catalysts utilized include $\text{Pd}(\text{PPh}_3)_4$ and $\text{PdCl}_2(\text{PPh}_3)_2$; Alternate solvents utilized include THF and pyrrolidine.

Alternate temperatures utilized include 70-100 °C. In some instances, water (1% v/v with respect to solvent) was added.

[00535] An alternate procedure has also been employed, especially with iodo-heterocycles: The appropriate alkynyl-trimethylsilane (2.1 equiv) was added to a degassed solution of TBAF (2.0 equiv, 0.5M in THF). After 5-30 min, the appropriate halo-heterocycle (1.0 equiv), CuI (0.05-0.3 equiv), and Pd(PPh₃)₄ (0.05-0.2 equiv) were added. The reaction was stirred at room temperature under N₂ for 2-24 hours (until complete by TLC or LCMS), then diluted with water, and extracted with an appropriate solvent. The extracts were combined, dried, filtered, concentrated, and then purified by silica gel column chromatography to give the alkynyl-heterocycle.

[00536] Note: Alternate catalysts utilized include PdCl₂(PPh₃)₂; Cosolvents utilized include triethylamine and pyrrolidine; When employing bromo-heterocycles, the reaction temperature was increased (80-120 °C).

General Procedure C: Multi-component cross-coupling of the alkynyl-heterocycles.



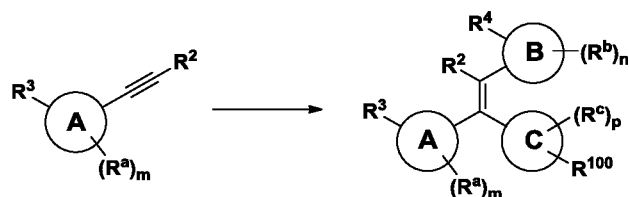
[00537] A mixture of the appropriate alkynyl-heterocycle (1.0 equiv), aryl- or heteroaryl-iodide (3.0 equiv), aryl- or heteroaryl-boronic acid (3.0 equiv), K₂CO₃ (3.0 equiv), and *N,N*-dimethylformamide (DMF)/water (2:1; 50 mL/mmol) was degassed with three vacuum/N₂ cycles and then heated at 45-50 °C. After 10 min (or when homogenous), a solution of Pd(PhCN)₂Cl₂ (0.01-0.02 equiv) in DMF was added (Note 1). The reaction was stirred at 45-50 °C for 4-24 h (until complete by TLC or LCMS; Note 2), allowed to cool to room temperature, quenched with water, and then extracted with ethyl acetate. The extracts were washed with water, washed with brine, dried, filtered, concentrated, and purified by silica gel chromatography to give the desired tetra-substituted alkene.

[00538] Note 1: In some instances, the Pd catalyst was added as a solid. In other instances, all chemicals were simply mixed at room temperature, degassed, and then heated. In still other instances, the boronic acid was added last as a DMF/water solution.

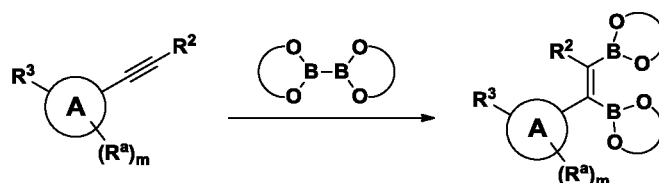
[00539] Note 2: When incomplete conversion of alkynyl-heterocycle was observed (especially with ortho-substituted aryl-iodides), additional aryl-iodide, aryl-boronic acid, and K₂CO₃

(1-3 equiv each) were added, and heating was continued for an additional 8-24 h. In some instances, this was repeated multiple times.

General Procedure D: Alternate multi-component cross-coupling of the alkynyl-heterocycles.



Step 1: Formation of bis(dioxaboryl)-alkene.



[00540] A solution of the appropriate alkynyl-heterocycle (1.0 equiv), bis(neopentylglycolato)diboron (1.1-1.2 equiv; Note 1), (η^2 -C₂H₄)Pt(PPh₃)₂ (0.02 equiv; Note 2), and solvent (2 mL/mmol; dioxane or 2-MeTHF; Note 3) was degassed with three vacuum/N₂ cycles and then refluxed (Note 4) under N₂ for 1-8 h (until complete by TLC or LCMS). The reaction was allowed to cool to room temperature and then either i) taken directly into Step 2; ii) concentrated to give a crude residue; or iii) concentrated and purified by silica gel chromatography to give the pure bis(dioxaboryl)-alkene.

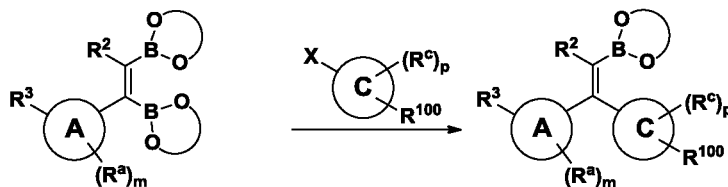
[00541] Note 1: With small R² groups such as ethyl, bis(pinacolato)diboron was more commonly utilized.

[00542] Note 2: In some instances, 0.002-0.05 equivalents of Pt catalyst have been utilized. Pt(PPh₃)₄ is an alternate catalyst. Pt(PPh₃)₄ with Pd(PPh₃)₄ is an alternate catalyst system.

[00543] Note 3: Alternate solvents utilized include DME, PhMe, or DMA.

[00544] Note 4: Alternate reaction temperatures utilized include 80-120 °C.

Step 2: Cross-coupling of the bis(dioxaboryl)-alkene.



[00545] A mixture of bis(dioxaboryl)-alkene (1.0 equiv), an appropriate aryl- or heteroaryl-halide (1.0 equiv), PdCl₂(PPh₃)₂ (0.1 equiv; Note 1), Cs₂CO₃ (2 equiv; Note 2), solvent (4 mL/mmol; dioxane or 2-MeTHF; Notes 3 & 4), and water (1% v/v; Note 5) was stirred vigorously at room temperature (Note 6) under N₂ (Note 7) for 1-24h (until complete by TLC or LCMS). The reaction was then either i) taken directly into Step 3; or ii) processed to isolate the 1-aryl-2-dioxaboryl-

alkene: [The reaction was diluted with ethyl ether (or ethyl acetate) and washed with water (1-3 times). The aqueous phases were back extracted with ethyl ether (or ethyl acetate). The extracts were combined, dried, filtered, concentrated and then purified by silica gel chromatography].

[00546] Note 1: In some instances, 0.02-0.2 equivalents of Pd catalyst have been utilized. Alternate catalysts utilized include PdCl₂(dppf).

[00547] Note 2: In some instances, 1.2-3 equivalents of Cs₂CO₃ have been utilized.

[00548] Note 3: Alternate solvents utilized include DME, PhMe, DMA.

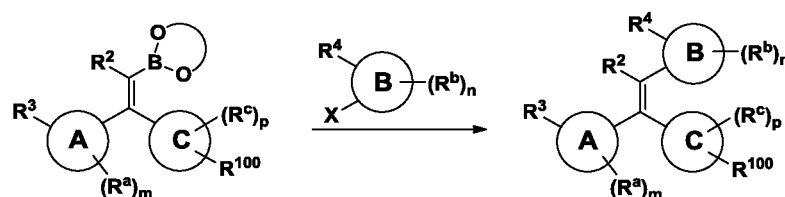
[00549] Note 4: When the bis(dioxaboryl)-alkene is brought into this step as a solution from Step 1, solvent (2 mL/mmol) is added to make the final volume of solvent approximately 4 mL/mmol.

[00550] Note 5: In some instances, additional water (0.5-1% v/v with respect to solvent) was added. In other instances, 0.5-3% water (v/v with respect to solvent) has been utilized.

[00551] Note 6: Alternate reaction temperatures utilized include 20-70 °C, commonly when the halide was bromo or chloro.

[00552] Note 7: In some instances, this reaction was degassed with three vacuum/N₂ cycles.

Step 3: Cross-coupling of the 1-aryl-2-dioxaboryl-alkene.



[00553] A mixture of 1-aryl-2-dioxaboryl-alkene (1.0 equiv), an appropriate aryl- or heteroaryl-halide (1.5 equiv; Note 1), PdCl₂(PPh₃)₂ (0.1 equiv; Note 2), solvent (4 mL/mmol: dioxane or 2-MeTHF; Notes 3 & 4), and KOH (4M, 6 equiv; Note 5) was degassed with three vacuum/N₂ cycles and then refluxed (Note 6) under N₂ for 1-24 h (until complete by TLC or LCMS). The reaction was allowed to cool to room temperature, diluted with ethyl ether (or ethyl acetate), and washed with water (1-3 times). The aqueous phases were back extracted with ethyl ether (or ethyl acetate). The extracts were combined, dried, filtered, concentrated and then purified by silica gel chromatography to give the desired tetra-substituted alkene.

[00554] Note 1: In some instances, 1.2-2.5 equivalents of aryl- or heteroaryl-halide were utilized.

[00555] Note 2: In some instances, 0.02-0.2 equivalents of Pd catalyst were utilized. Alternate catalysts utilized include PdCl₂(dppf) and Pd(PPh₃)₄.

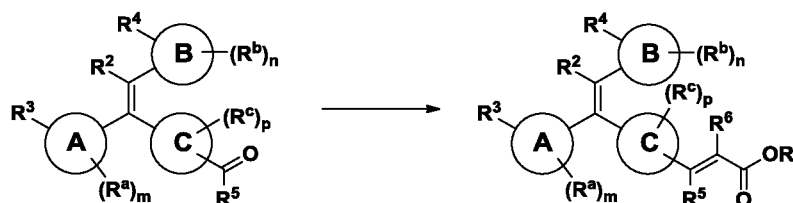
[00556] Note 3: Alternate solvents utilized include DME, DMF, DMA, DMSO.

[00557] Note 4: When the 1-aryl-2-dioxaboryl-alkene is brought into this step directly from Step 2, no additional solvent or $\text{PdCl}_2(\text{PPh}_3)_2$ was added. Only the aryl- or heteroaryl-halide and KOH were added.

[00558] Note 5: In some instances, 4-7 equiv of KOH were utilized, and the aqueous solution of KOH was 3-6M. For some compounds, especially those with sensitive functionality, K_2CO_3 (6 equiv, 4M aqueous) was used in place of KOH, and DMSO was used as either the sole solvent or a co-solvent (typically 1:1; 2-MeTHF:DMSO).

[00559] Note 6: Alternate reaction temperatures utilized include 70-120 °C.

General Procedure E: Olefination of the tetrasubstituted-alkene, aryl- or heteroaryl-aldehydes.



[00560] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1-1.4 equiv) was added dropwise to a mixture of the appropriate aryl-aldehyde (1.0 equiv), triethylphosphonoacetate (1.1-1.5 equiv; Note 1), lithium chloride (2.0 equiv), and anhydrous acetonitrile (2 mL/mmol) at room temperature. The resulting mixture was stirred for 1-4 h (until complete by TLC or LCMS; Note 2), concentrated, and then either i) purified by silica gel chromatography; or ii) resuspended in dichloromethane (or ethyl acetate or ether), washed with water, washed with brine, dried, filtered, concentrated, and then purified by silica gel chromatography to give the desired acrylic ester.

[00561] Note 1: In some instances, alternate phosphonate reagents were utilized to give the desired alkene. For example: *tert*-butyl diethylphosphonoacetate; diethyl ((1-trityl-1H-imidazol-4-yl)methyl)phosphonate; diethyl (cyanomethyl)phosphonate; diethyl(pyridin-2-ylmethyl)phosphonate.

[00562] Note 2: Alternate reaction conditions: 1-2 equivalents of phosphonate in THF at -78 °C or 0 °C were treated with *n*-BuLi, *t*-BuOK or NaH (1-2 equiv). Then aldehyde (1 equiv) was added, and the reaction was continued at -78 °C, 0 °C, or room temperature until complete by TLC and/or LCMS.

General Procedure F: Removal of the protecting group.

[00563] Removing THP: Variant I: A solution of HCl (Note 1) was added to a solution of the protected-heterocycle (1.0 equiv) in ethanol (2-5 mL/mmol; Note 2) at room temperature. The mixture was heated at 70-90 °C for 2-24 h (until complete by TLC or LCMS).

[00564] Variant II: A 4M solution of HCl in dioxane (4-10 mL/mmol; Note 3) was added to the protected-heterocycle (1.0 equiv) at room temperature. The mixture was heated at 50-90 °C (Note 4) for 2-18 h (until complete by TLC or LCMS).

[00565] Variant III: A solution of trifluoroacetic acid and dichloromethane (1:1; 4-10 mL/mmol) was added to the protected-heterocycle (1.0 equiv; Note 5) at room temperature. The mixture was stirred at room temperature for 1-4 h (until complete by TLC or LCMS).

[00566] For each Variant (Note 6), the reaction was allowed to cool to room temperature and then either i) simply concentrated or ii) diluted with ethyl acetate, washed with water (1-3 times), dried, filtered, and concentrated. The crude product was then either i) carried on directly to the next step or ii) purified by silica gel chromatography or reverse-phase HPLC.

[00567] Note 1: Most commonly, 2M HCl in diethyl ether or 1.25M HCl in ethanol were used, and the volume of HCl solution was 10% of the solvent volume.

[00568] Note 2: In some instances, methanol or isopropanol were utilized.

[00569] Note 3: In some instances, the 4M HCl solution was diluted to 2M with water.

[00570] Note 4: Alternate reaction temperatures utilized include 50-100 °C.

[00571] Note 5: In some instances, the protected-heterocycle was added to the TFA/DCM solution.

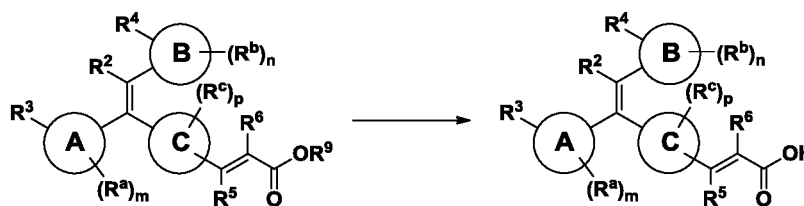
[00572] Note 6: When the protected heterocycle contained a t-butyl ester: Variant I provided the ethyl ester; Variants II & III provided the carboxylic acid.

[00573] Removing Trityl: TFA/DCM (1:2) at rt for 2-8 h.

[00574] Removing BOC: TFA/DCM (1:4) at rt for 0.5-4 h.

[00575] Other protecting groups (acetyl, MOM, SEM) were removed under standard conditions.

General Procedure G: Hydrolysis of the acrylic ester to the acrylic acid.



[00576] A 2M aqueous solution of LiOH (10 equiv; Note 1) was added to a solution of the appropriate ester (1.0 equiv) in ethanol/tetrahydrofuran (1:1, 10 mL/mmol; Note 2) at room temperature, and the mixture was stirred for 4-24 h (until complete by TLC or LCMS). A solution of HCl (1M aqueous) was added until pH ~ 3 (Note 3). The mixture was diluted with water and extracted with ethyl acetate (or dichloromethane or ether). The organic layer was washed with water, washed with brine, dried, filtered, concentrated, and purified by silica gel chromatography or reverse-phase HPLC to give the desired acrylic acid.

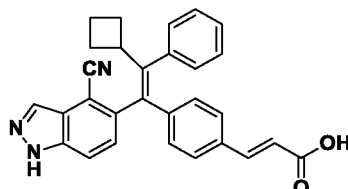
[00577] Note 1: In some instances, 2.0-30 equivalents of LiOH were utilized. In some instances, the LiOH was dissolved in a minimum amount of water. In some instances, NaOH or KOH was used.

[00578] Note 2: In some instances, a single solvent (ethanol, dioxane, or tetrahydrofuran) was used.

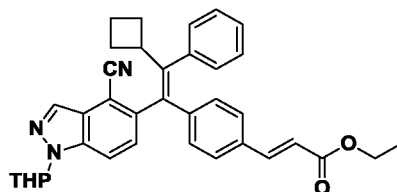
[00579] Note 3: Alternate work-up procedures have been employed including: i) the use of sat'd NH₄Cl in place of aqueous HCl and ii) removal of the organic solvent by rotary evaporation prior to acid quench.

Example 1

(E)-3-(4-((E)-1-(4-Cyano-1*H*-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid

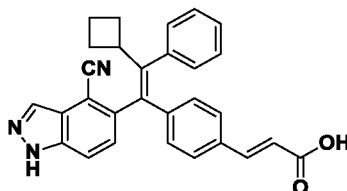


Step 1: (E)-Ethyl 3-(4-((E)-1-(4-cyano-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylate



[00580] A solution of 5-(cyclobutylethynyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-4-carbonitrile (201 mg, 0.66 mmol, Intermediate 24), (E)-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)boronic acid (440 mg, 2.0 mmol), iodobenzene (0.20 mL, 1.8 mmol), K₂CO₃ (276 mg, 2.0 mmol), and DMF/H₂O (2:1, 33 mL) was degassed with three vacuum/N₂ cycles, and then Pd(PhCN)₂Cl₂ (5.2 mg, 0.014 mmol) was added. The reaction was heated at 50 °C for 6 hrs, allowed to cool to rt, and diluted with EtOAc (~100 mL). This mixture was washed with water (3 x 100 mL), washed with brine (100 mL), dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (0% - 20% EtOAc in hexanes) to give (E)-ethyl 3-(4-((E)-1-(4-cyano-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylate (270 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.36 (s, 1H), 8.16 (d, 1H), 7.53 (d, 1H), 7.43 (d, 1H), 7.38 (d, 2H), 7.34-7.28 (m, 2H), 7.25-7.18 (m, 3H), 7.00 (d, 2H), 6.44 (d, 1H), 5.98 (d, 1H), 4.13 (q, 2H), 3.94-3.85 (m, 1H), 3.82-3.72 (m, 1H), 3.29-3.18 (m, 1H), 2.47-2.35 (m, 1H), 2.10-2.00 (m, 2H), 1.94-1.70 (m, 4H), 1.70-1.51 (m, 4H), 1.40-1.30 (m, 1H), 1.21 (t, 3H). LCMS: 474 [(M-THP+H)+H]⁺.

Step 2: (E)-3-(4-((E)-1-(4-Cyano-1*H*-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid

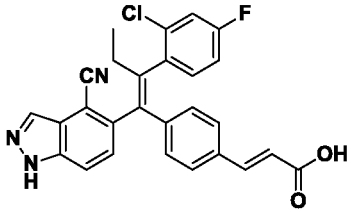
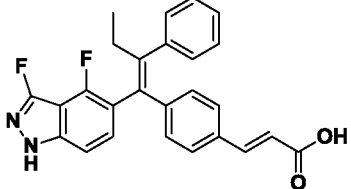
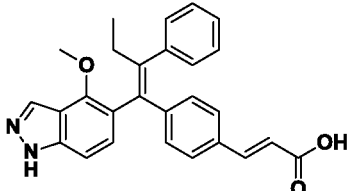
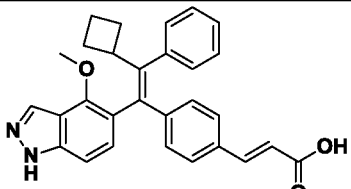
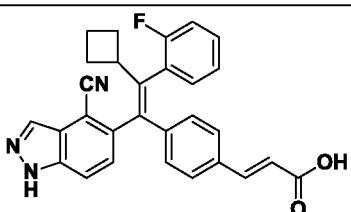
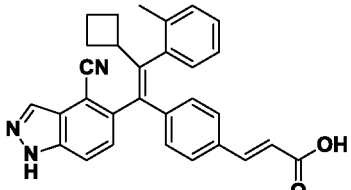
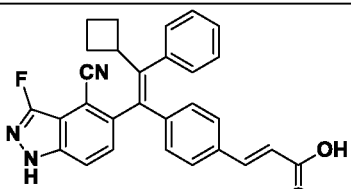
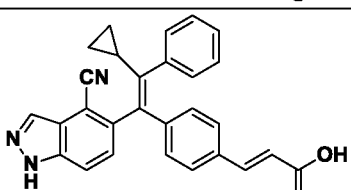


[00581] A 2M solution of HCl in diethyl ether (0.70 mL) was added to (E)-ethyl 3-(4-((E)-1-(4-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylate (270 mg, 0.48 mmol) in EtOH (7 mL). The solution was heated at 70 °C for 75 min, allowed to cool to rt, concentrated, and dried under vacuum. To this crude material, THF (2 mL), EtOH (2 mL) and 2M LiOH (2 mL, 4 mmol) was added. The resulting mixture was stirred at rt for 5.5 hrs, and then additional 2M LiOH (0.6 mL, 1.2 mmol) was added. The reaction was stirred for an additional 1.5 hrs, diluted with EtOAc and water, and then acidified to pH ~ 5 with 1M HCl. The layers were separated, and the EtOAc extract was dried (MgSO₄), filtered, concentrated, and purified by reverse-phase HPLC to give the title compound as a white solid (105 mg). ¹H NMR (400MHz, DMSO-d₆): δ 13.73 (bs, 1H), 12.28 (bs, 1H), 8.31 (s, 1H), 7.95 (d, 1H), 7.44 (d, 1H), 7.41-7.27 (m, 5H), 7.24-7.18 (m, 3H), 7.00 (d, 2H), 6.34 (d, 1H), 3.29-3.18 (m, 1H), 1.90-1.49 (m, 5H), 1.40-1.31 (m, 1H). LCMS: 446 (M+H)⁺.

[00582] The Examples in Table 8 were prepared from alkyne intermediates following General Procedures C, F (optionally), & G. The alkyne intermediates have either i) been described herein or ii) were prepared from known or commercially available halo-heterocycles following General Procedures A (optionally) & B.

Table 8.

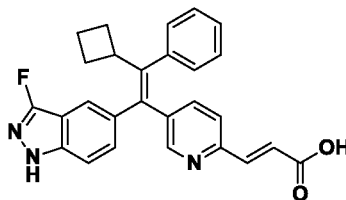
Example	Name	Structure	LCMS [M+H] ⁺
2	(E)-3-(4-((E)-1-(4-Chloro-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid		455
3	(E)-3-(4-((E)-1-(4-Cyano-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		420
4	(E)-3-(4-((E)-2-Cyclobutyl-1-(1-oxoisindolin-5-yl)-2-phenylvinyl)phenyl)acrylic acid		436
5	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1-oxoisindolin-5-yl)vinyl)phenyl)acrylic acid		488

Example	Name	Structure	LCMS [M+H] ⁺
6	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-1 <i>H</i> -indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		472
7	(E)-3-(4-((E)-1-(3,4-Difluoro-1 <i>H</i> -indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		431
8	(E)-3-(4-((E)-1-(4-Methoxy-1 <i>H</i> -indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		425
9	(E)-3-(4-((E)-2-Cyclobutyl-1-(4-methoxy-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		451
10	(E)-3-(4-((E)-1-(4-Cyano-1 <i>H</i> -indazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid		464
11	(E)-3-(4-((E)-1-(4-Cyano-1 <i>H</i> -indazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid		460
12	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1 <i>H</i> -indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid		464
13	(E)-3-(4-((E)-1-(4-Cyano-1 <i>H</i> -indazol-5-yl)-2-cyclopropyl-2-phenylvinyl)phenyl)acrylic acid		432

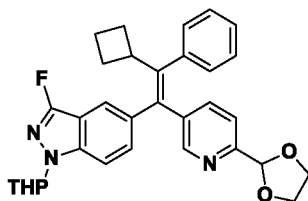
Example	Name	Structure	LCMS [M+H] ⁺
14	(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1 <i>H</i> -indazol-5-yl)-2-cyclopropyl-2-phenylvinyl)phenyl)acrylic acid		450
15	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-3-methyl-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		425 [M-H] ⁻
16	(E)-3-(4-((E)-2-(4-Chloro-2-fluorophenyl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-3-methylbut-1-en-1-yl)phenyl)acrylic acid		477 [M-H] ⁻
17	(E)-3-(4-((E)-1-(1 <i>H</i> -Benzo[d][1,2,3]triazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid		422
18	(E)-3-(4-((E)-2-Cyclobutyl-1-(1 <i>H</i> -indazol-4-yl)-2-phenylvinyl)phenyl)acrylic acid		421
19	(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		437
20	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-3-methyl-2-(4-methylthiophen-3-yl)but-1-en-1-yl)phenyl)acrylic acid		446
21	(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid		463

Example	Name	Structure	LCMS [M+H] ⁺
22	(E)-3-(4-((E)-2-Cyclobutyl-1-(4,7-difluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		457
23	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid		467 [M-H] ⁻
24	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid		467 [M-H] ⁻
25	(E)-3-(4-((E)-2-Cyclobutyl-1-(4-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		439
26	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		425
27	(E)-3-(4-((E)-2-Cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-2-phenylvinyl)phenyl)acrylic acid		436 [M-H] ⁻
28	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)vinyl)phenyl)acrylic acid		488 [M-H] ⁻
29	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid		437 [M-H] ⁻

Example	Name	Structure	LCMS [M+H] ⁺
30	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid		455
31	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid		453 [M-H] ⁻
32	(E)-3-(4-((E)-1-(4,7-Difluoro-1 <i>H</i> -indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid		431
33	(E)-3-(4-((E)-2-Cyclobutyl-2-phenyl-1-(1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-5-yl)vinyl)phenyl)acrylic acid		422
34	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-5-yl)vinyl)phenyl)acrylic acid		474
35	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(1 <i>H</i> -indazol-5-yl)-3-methylbut-1-en-1-yl)phenyl)acrylic acid		443

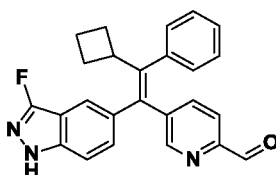
Example 36**(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylic acid**

Step 1: (Z)-5-(1-(6-(1,3-Dioxolan-2-yl)pyridin-3-yl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



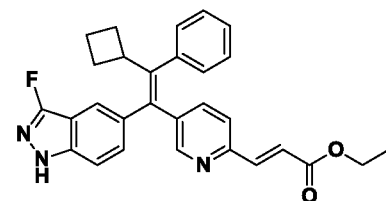
[00583] The title compound was prepared from 5-(cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate 14), iodobenzene, and (6-(1,3-dioxolan-2-yl)pyridin-3-yl)boronic acid following General Procedure C. LCMS: 526 (M+H)⁺.

Step 2: (Z)-5-(2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)picolinaldehyde



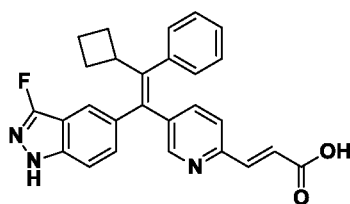
[00584] (Z)-5-(1-(6-(1,3-Dioxolan-2-yl)pyridin-3-yl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (0.5 g, 0.95 mmol) was suspended in 4M HCl in dioxane (2.5 mL) and diluted with water (2.5 mL). This mixture was heated at 80 °C for 4h, cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified on a silica gel column (0-50% hexanes-ethyl acetate) to afford the title compound as yellow film. LCMS: 398 (M+H)⁺.

Step 3: (E)-Ethyl 3-(5-((Z)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylate



[00585] Neat DBU (0.11 mL, 0.73 mmol) was added dropwise to a mixture of (Z)-5-(2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)picolinaldehyde (0.13 g, 0.33 mmol), triethylphosphonoacetate (0.16 mL, 0.785 mmol), lithium chloride (0.056 g, 1.32 mmol), and anhydrous acetonitrile (3.3 mL). The resulting mixture was stirred at room temperature for 30 minutes, concentrated, resuspended in DCM, washed with water, washed with brine, dried over sodium sulfate, filtered, and concentrated to afford the title compound. LCMS: 468 (M+H)⁺.

Step 4: (E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylic acid

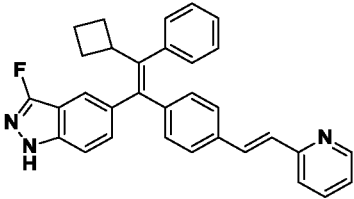


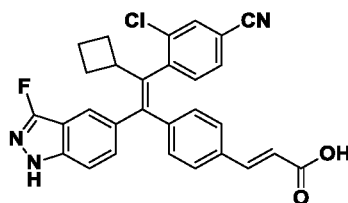
[00586] A 2M aqueous solution of LiOH (0.8 mL, 1.6 mmol) was added to a solution of (E)-ethyl 3-(5-((Z)-2-cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylate (0.15 g, 0.32 mmol) in THF-EtOH (1:1, 6.4 mL) at room temperature. The resulting mixture was stirred for 6 h and then quenched with 1N aqueous HCl until the pH was 3. This mixture was diluted with water and then extracted with ethyl acetate. The organic layer was washed with water, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was dissolved in ethyl ether (3 mL), and then HCl (0.5 mL, 2M solution in Et₂O) was added. After a few minutes of sonication, the solids were filtered and dried to give the title compound as an HCl salt. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.65 (s, 1H), 8.20 (d, 1H), 7.61 (s, 1H), 7.52 (dd, 1H), 7.46-7.33 (m, 3H), 7.30-7.26 (m, 3H), 7.20-7.10 (m, 3H), 6.66 (d, 1H), 3.47-3.35 (m, 1H), 1.88-1.75 (m, 4H), 1.65-1.60 (m, 1H), 1.39-1.33 (m, 1H); LCMS: 440 (M+H)⁺.

[00587] The Examples in Table 9 were prepared from the appropriate boronic acid and phosphonate following the procedures outlined for Example 36 or in General Procedures C, E, F & G (optionally).

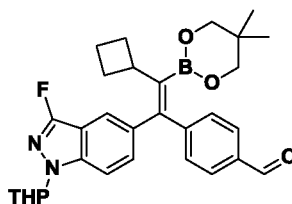
Table 9.

Example	Name	Structure	LCMS [M+H] ⁺
37	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-2-methylphenyl)acrylic acid		453
38	(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-3-methoxyphenyl)acrylic acid		469
39	5-((E)-1-(4-((E)-2-(1 <i>H</i> -Imidazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1 <i>H</i> -indazole		461

Example	Name	Structure	LCMS [M+H] ⁺
215	(5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-2-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole		472

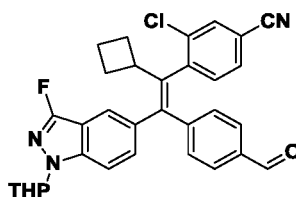
Example 40**(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid**

Step 1: (Z)-4-(2-Cyclobutyl-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)benzaldehyde



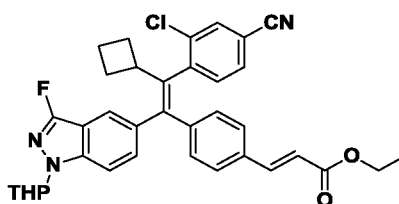
[00588] A solution of 5-(cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.19 g, 4.0 mmol, Intermediate 14), bis(neopentylglycolato)diboron (0.94 g, 4.17 mmol), Pt(PPh₃)₄ (0.10 g, 0.08 mmol), and 2-methyltetrahydrofuran (16 mL) was degassed with three vacuum/N₂ cycles, heated at 85 °C under N₂ for 3.5 h, and then allowed to cool to room temperature. 4-Iodobenzaldehyde (0.945 g, 4.07 mmol), cesium carbonate (2.7 g, 8.3 mmol), and PdCl₂(PPh₃)₂ (0.25 g, 0.36 mmol) were added, and the reaction was stirred vigorously at rt. After 1.5 h, water (0.08 mL, 0.5% v/v) was added. After an additional 15 h, the reaction was diluted with ethyl ether (25 mL) and washed with water (40 mL). The aqueous wash was extracted with ethyl ether (40 mL). The extracts were combined, dried, filtered, concentrated, and then purified by silica gel chromatography (1:0→3:2; hexanes: ethyl acetate) to give (Z)-4-(2-cyclobutyl-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)benzaldehyde as a mixture of regioisomers. Data for major regioisomer: ¹H NMR (400 MHz, DMSO-d₆): δ 9.95 (s, 1H), 7.81 (d, 2H), 7.73 (d, 1H), 7.37-7.30 (m, 3H), 7.17 (dd, 1H), 5.79 (dd, 1H), 3.92-3.85 (m, 1H), 3.77-3.68 (m, 1H), 3.52 (s, 4H), 3.18-3.08 (m, 1H), 2.32-2.18 (m, 1H), 2.18-2.05 (m, 2H), 2.05-1.92 (m, 2H), 1.92-1.80 (m, 2H), 1.80-1.60 (m, 3H), 1.60-1.48 (2H), 0.86 (s, 6H).

Step 2: (E)-3-Chloro-4-(1-cyclobutyl-2-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(4-formylphenyl)vinyl)benzonitrile



[00589] A mixture of (Z)-4-(2-cyclobutyl-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)benzaldehyde (303 mg, 0.59 mmol), 4-bromo-3-chlorobenzonitrile (196 mg, 0.91 mmol), PdCl₂(PPh₃)₂ (49 mg, 0.070 mmol), 2-methyl THF (1.2 mL), DMSO (1.2 mL), and 4M aq. K₂CO₃ (0.9 mL, 3.6 mmol) was degassed with three vacuum/N₂ cycles and heated at 85 °C for 2.5 h. The reaction was allowed to cool to rt, diluted with Et₂O, washed with water (30 mL), and washed with brine (30 mL). Each aqueous layer was back extracted with Et₂O. The combined Et₂O extracts were dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (0%-25% EtOAc in hexanes) to give (E)-3-chloro-4-(1-cyclobutyl-2-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(4-formylphenyl)vinyl)benzonitrile as a yellow foam (171 mg). ¹H NMR (400MHz, DMSO-d₆): δ 9.81 (s, 1H), 7.99 (d, 1H), 7.82-7.76 (m, 2H), 7.64-7.58 (m, 4H), 7.42-7.37 (m, 1H), 7.24 (d, 2H), 5.80 (d, 1H), 3.91-3.85 (m, 1H), 3.77-3.68 (m, 1H), 3.49-3.38 (m, 1H), 2.34-2.20 (m, 1H), 2.06-1.91 (m, 3H), 1.90-1.78 (m, 3H), 1.69-1.60 (m, 2H), 1.60-1.51 (m, 2H), 1.45-1.34 (m, 1H). LCMS: 540 (M+H)⁺.

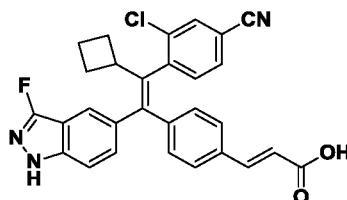
Step 3: (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)acrylate



[00590] 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.070 mL, 0.47 mmol) was added dropwise to a mixture of (E)-3-chloro-4-(1-cyclobutyl-2-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(4-formylphenyl)vinyl)benzonitrile (167 mg, 0.31 mmol), triethyl phosphonoacetate (0.12 mL, 0.62 mmol), lithium chloride (31 mg, 0.73 mmol), and acetonitrile (1.5 mL). The reaction was stirred at rt for 3 h, diluted with DCM, washed with water (20 mL), and then washed with brine (20 mL). Each aqueous layer was back extracted with DCM. The combined DCM extracts were dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (0%-20% EtOAc in hexanes) to give (E)-ethyl 3-(4-((E)-2-(2-chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)acrylate as an off white solid (142 mg). ¹H

NMR (400MHz, DMSO- d_6): δ 8.00 (d, 1H), 7.78 (dd, 2H), 7.62-7.56 (m, 2H), 7.48-7.39 (m, 3H), 7.39-7.34 (m, 1H), 7.03 (d, 2H), 6.47 (d, 1H), 5.81 (d, 1H), 4.13 (q, 2H), 3.91-3.85 (m, 1H), 3.78-3.68 (m, 1H), 3.46-3.34 (m, 1H), 2.35-2.19 (m, 1H), 2.06-1.91 (m, 3H), 1.87-1.77 (m, 3H), 1.67-1.51 (m, 4H), 1.44-1.33 (m, 1H), 1.21 (t, 3H). LCMS: 610 (M+H)⁺.

Step 4: (E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)vinyl)phenyl)acrylic acid



[00591] A 2M solution of HCl in diethyl ether (0.32 mL) was added to a solution of (E)-ethyl 3-(4-((E)-2-(2-chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)vinyl)phenyl)acrylate (138 mg, 0.23 mmol) and ethanol (3.2 mL). The reaction was heated at 70 °C for 24.5 h, allowed to cool to rt, concentrated, and dried under vacuum. To this crude material, THF (1 mL), EtOH (1 mL) and 2M LiOH (0.6 mL, 1.2 mmol) were added. The resulting mixture was stirred at rt for 5 h, diluted with EtOAc and water, and then acidified to pH ~ 2 with 1M HCl. The layers were separated, and the EtOAc extract was dried (MgSO₄), filtered, concentrated, and purified by reverse-phase HPLC to give the title compound as an off-white solid (39 mg). ¹H NMR (400MHz, DMSO- d_6): δ 12.64 (s, 1H), 7.99 (d, 1H), 7.77 (dd, 1H), 7.59-7.54 (m, 2H), 7.51 (dd, 1H), 7.43-7.35 (m, 3H), 7.27 (dd, 1H), 7.03 (d, 2H), 6.37 (d, 1H), 3.48-3.37 (m, 1H), 1.90-1.75 (m, 3H), 1.69-1.56 (m, 2H), 1.44-1.33 (m, 1H). LCMS: 498 (M+H)⁺.

[00592] The Examples in Table 10 were prepared from alkyne intermediates following General Procedures D, E, F (optionally), & G. The alkyne intermediates have either i) been described herein or ii) were prepared from known or commercially available halo-heterocycles following General Procedures A (optionally) & B.

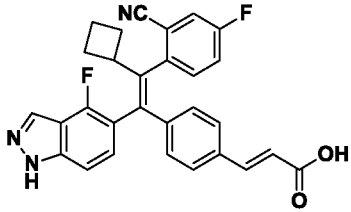
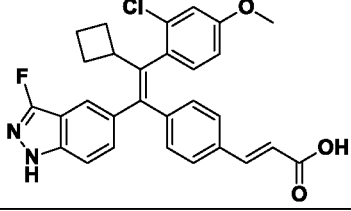
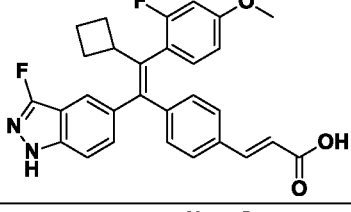
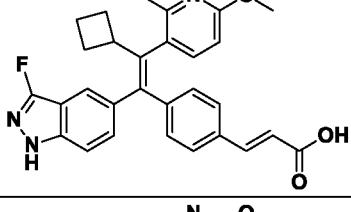
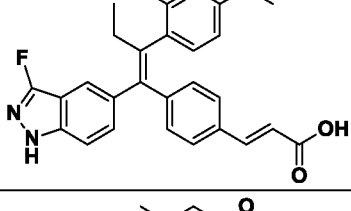
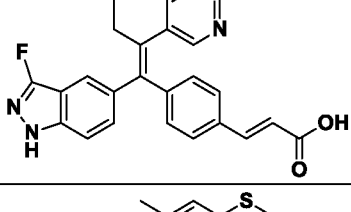
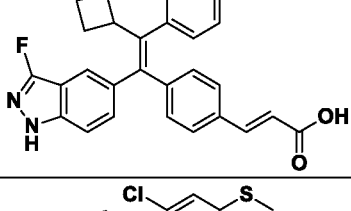
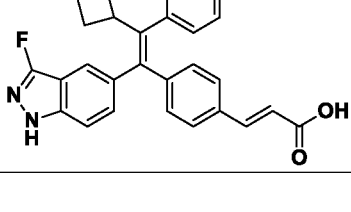
Table 10.

Example	Name	Structure	LCMS [M+H] ⁺
41	(E)-3-(4-((E)-1-(1 <i>H</i> -Indazol-5-yl)-2-(3-((trifluoromethyl)sulfonyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid		527

Example	Name	Structure	LCMS [M+H] ⁺
42	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		476
43	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		480
44	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		494
45	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-((trifluoromethyl)sulfonyl)phenyl)vinyl)phenyl)acrylic acid		569 [M-H] ⁻
46	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid		454
47	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-4-yl)vinyl)phenyl)acrylic acid		508
48	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		482
49	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		482

Example	Name	Structure	LCMS [M+H] ⁺
50	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		478
51	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-fluoro-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid		535
52	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-fluoropyridin-4-yl)vinyl)phenyl)acrylic acid		458
53	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		464
54	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		464
55	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		460
56	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-((6-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid		585
57	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid		585

Example	Name	Structure	LCMS [M+H] ⁺
58	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-((6-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid		585
59	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid		585
60	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclobutyl-1-(4-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		480 [M-H] ⁻
61	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(4-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		498
62	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,4-dicyanophenyl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		487 [M-H] ⁻
63	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxy-2-methylphenyl)but-1-en-1-yl)phenyl)acrylic acid		457
64	(E)-3-(4-((E)-2-Cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid		465
65	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid		483

Example	Name	Structure	LCMS [M+H] ⁺
66	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclobutyl-1-(4-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		482
67	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		503
68	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid		487
69	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxy-2-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		484
70	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxy-2-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid		458
71	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid		458
72	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methyl-4-(methylthio)phenyl)vinyl)phenyl)acrylic acid		497 [M-H] ⁻
73	(E)-3-(4-((E)-2-(2-Chloro-4-(methylthio)phenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		517 [M-H] ⁻

Example	Name	Structure	LCMS [M+H] ⁺
74	(E)-3-(4-((E)-2-(3-Cyanopyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		465
75	(E)-3-(4-((E)-1-(Benzofuran-2-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		471 [M-H] ⁻
76	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylic acid		501 [M-H] ⁻
77	(E)-3-(4-((E)-1-(Benzofuran-2-yl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		456
78	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylic acid		486
79	(E)-3-(4-((E)-1-(1 <i>H</i> -Benzo[d][1,2,3]triazol-5-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		474
80	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-4-yl)vinyl)phenyl)acrylic acid		473
81	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methoxypyridin-4-yl)vinyl)phenyl)acrylic acid		470

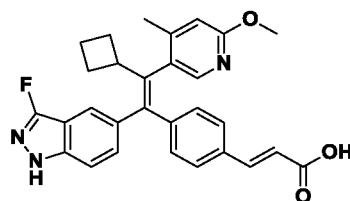
Example	Name	Structure	LCMS [M+H] ⁺
82	(E)-3-(4-((E)-2-(4-Cyanothiophen-3-yl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		470
83	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid		453
84	(E)-3-(4-((E)-2-(3-(1 <i>H</i> -Pyrazol-1-yl)phenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		505
85	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		483
86	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid		458
87	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-(pyrrolidin-1-yl)phenyl)vinyl)phenyl)acrylic acid		508
88	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyanothiophen-3-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		469
89	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methoxy-3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid		484

Example	Name	Structure	LCMS [M+H] ⁺
90	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		481
91	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid		468
92	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid		468
93	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid		469
94	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid		456
95	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		481
96	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-methylphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		477
97	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		493

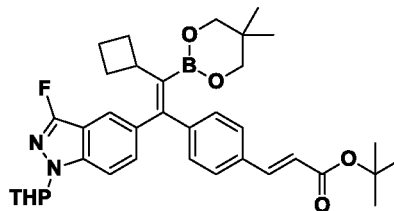
Example	Name	Structure	LCMS [M+H] ⁺
98	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid		453
99	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid		457
100	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		473
101	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		472
102	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		456
103	((E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		506
104	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		456
105	((E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		452

Example	Name	Structure	LCMS [M+H] ⁺
106	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		472
107	((E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		468
108	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		498
109	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		480
110	(E)-3-(4-((E)-2-Cyclobutyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		498
111	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methoxy-4-(trifluoromethyl)pyrimidin-5-yl)vinyl)phenyl)acrylic acid		539
216	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		485
217	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid		481 [M-H] ⁻

Example	Name	Structure	LCMS [M+H] ⁺
218	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		497
219	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		497

Example 112**(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid**

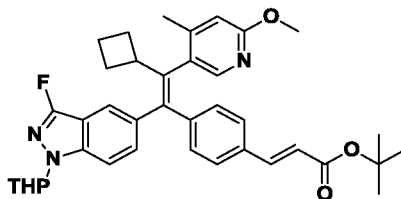
Step 1: (E)-*tert*-Butyl 3-(4-((*Z*)-2-cyclobutyl-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)vinyl)phenyl)acrylate



[00593] A solution of 5-(cyclobutylethynyl)-3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (3.51 g, 11.8 mmol; Intermediate 14), bis(neopentylglycolato)diboron (2.81 g, 12.4 mmol), ethylenebis(triphenyl phosphine)platinum (176 mg, 0.24 mmol), and anhydrous dioxane (23.5 mL) was degassed with three vacuum/N₂ cycles and then heated at 100 °C for 3.5 h. Additional bis(neopentyl glycolato)diboron (269 mg, 1.19 mmol) was added, and the reaction was heated at 100 °C for 1.5 h and then allowed to cool to rt. (E)-*tert*-Butyl 3-(4-iodophenyl)acrylate (3.92g, 11.9 mmol; Intermediate 45), Cs₂CO₃ (7.67g, 23.5 mmol), PdCl₂(PPh₃)₂ (831 mg, 1.18 mmol), dioxane (23.5 mL), and water (0.47 mL) were added. The reaction was degassed with three vacuum/N₂ cycles, stirred at rt for 3 h, diluted with EtOAc, washed with water (100 mL), and then washed with brine (100 mL). Each aqueous layer was back extracted with EtOAc, and the combined organic extracts were dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (0%-12% EtOAc in hexanes) to give (E)-*tert*-butyl 3-(4-((*Z*)-2-cyclobutyl-2-(5,5-dimethyl-1,3,2-

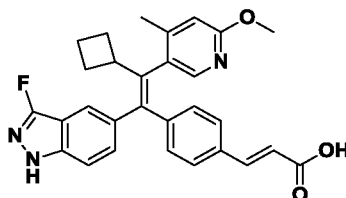
dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)vinyl)phenyl)acrylate as a mixture of regioisomers. Data for major regioisomer: ¹H NMR (400MHz, DMSO-*d*₆): δ 7.71 (d, 1H), 7.57 (d, 2H), 7.49 (d, 1H), 7.32 (s, 1H), 7.17-7.12 (m, 3H), 6.44 (d, 1H), 5.78 (d, 1H), 3.92-3.84 (m, 1H), 3.77-3.67 (m, 1H), 3.51 (s, 4H), 3.15-3.03 (m, 1H), 2.32-2.20 (m, 1H), 2.16-1.90 (m, 4H), 1.90-1.79 (m, 2H), 1.79-1.60 (m, 3H), 1.60-1.52 (m, 2H), 1.47 (s, 9H), 0.86 (s, 6H).

Step 2: (E)-*tert*-Butyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylate



[00594] A mixture of (E)-*tert*-butyl 3-(4-((Z)-2-cyclobutyl-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)vinyl)phenyl)acrylate (2.04 g, 3.33 mmol), 5-bromo-2-methoxy-4-methylpyridine (1.34 g, 6.64 mmol), PdCl₂(PPh₃)₂ (234 mg, 0.33 mmol), 2-methyl THF (13 mL), and 4M aq. KOH (4.7 mL, 18.8 mmol) was degassed with three vacuum/ N₂ cycles and then heated at 85 °C for 8 h. The reaction was allowed to cool to rt, diluted with EtOAc (50 mL), washed with water (50 mL), and then washed with brine (50 mL). Each aqueous layer was back extracted with EtOAc (50 mL), and the combined organic extracts were dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (0% - 2.5% EtOAc in DCM) to give (E)-*tert*-butyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylate as a yellow foam (964 mg). ¹H NMR (400MHz, DMSO-*d*₆): δ 7.90 (s, 1H), 7.77 (d, 1H), 7.60 (bs, 1H), 7.39-7.33 (m, 4H), 6.97 (d, 2H), 6.57 (s, 1H), 6.35 (d, 1H), 5.49 (d, 1H), 3.92-3.86 (m, 1H), 3.79 (s, 3H), 3.77-3.70 (m, 1H), 3.43-3.33 (m, 1H), 2.34-2.20 (m, 1H), 2.12 (s, 3H), 2.06-1.91 (m, 3H), 1.91-1.83 (m, 1H), 1.83-1.67 (m, 3H), 1.61-1.51 (m, 4H), 1.43 (s, 9H). LCMS: 624 (M+H)⁺.

Step 3: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid



[00595] (E)-*tert*-Butyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylate (480 mg, 0.77 mmol) was added portionwise to a solution of TFA/DCM (1:1, 7.5 mL) at rt. The reaction was stirred at rt for 6 h, concentrated (rotovap bath at 10 °C), and then dried under vacuum. The crude product was

purified by reverse-phase HPLC to give the title compound as a yellow solid (279 mg). ^1H NMR (400MHz, DMSO- d_6): δ 12.61 (s, 1H), 7.91 (s, 1H), 7.57 (bs, 1H), 7.50 (dd, 1H), 7.43-7.35 (m, 3H), 7.26 (dd, 1H), 6.99 (d, 2H), 6.60 (s, 1H), 6.36 (d, 1H), 3.80 (s, 3H), 3.46-3.35 (m, 1H), 2.14 (s, 3H), 1.92-1.70 (m, 3H), 1.68-1.50 (m, 2H), 1.43-1.34 (m, 1H). LCMS: 484 ($\text{M}+\text{H}$) $^+$.

[00596] The Examples in Table 11 were prepared from alkyne intermediates and acrylic-ester Intermediates following General Procedures D, F (optionally), & G (optionally). The alkyne intermediates have either i) been described herein or ii) were prepared from known or commercially available halo-heterocycles following General Procedures A (optionally) & B. The acrylic-ester Intermediates have been described herein.

Table 11.

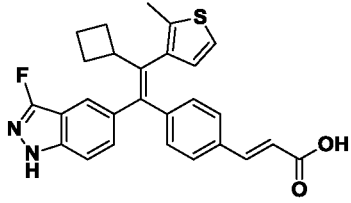
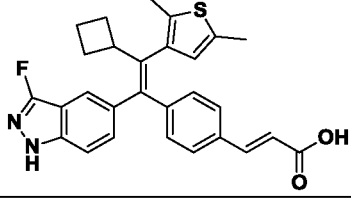
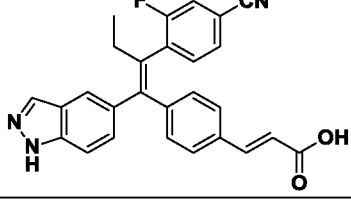
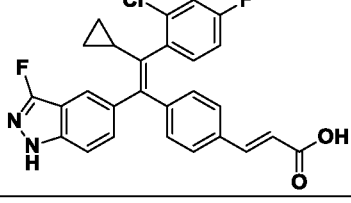
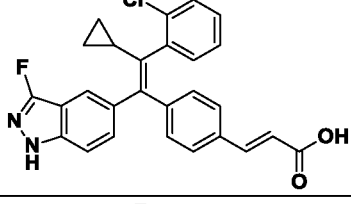
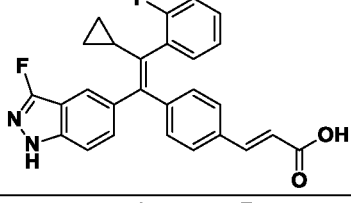
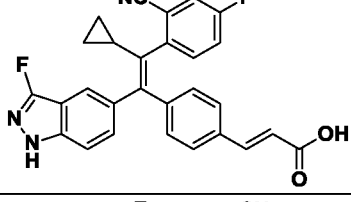
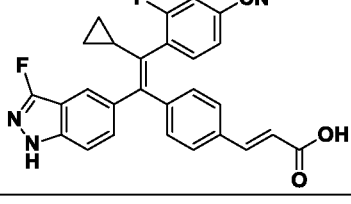
Example	Name	Structure	LCMS [$\text{M}+\text{H}$] $^+$
113	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid		473
114	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		489
115	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid		469
116	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		470
117	(E)-3-(4-((E)-2-Cyclopropyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		484

Example	Name	Structure	LCMS [M+H] ⁺
118	(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		464
119	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		484
120	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		484
121	(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		480
122	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)vinyl)phenyl)acrylic acid		611
123	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid		457
124	(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		473
125	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid		453

Example	Name	Structure	LCMS [M+H] ⁺
126	(E)-3-(4-((E)-2-Cyclobutyl-1-(1 <i>H</i> -indazol-4-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid		441
127	(E)-3-(4-((E)-2-Cyclobutyl-1-(1 <i>H</i> -indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		466
128	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(pyridin-3-yl)vinyl)phenyl)acrylic acid		440
129	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(5-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		454
130	(E)-3-(4-((E)-2-(5-Chloropyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		474
131	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(5-fluoropyridin-3-yl)vinyl)phenyl)acrylic acid		458
132	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(5-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid		470

Example	Name	Structure	LCMS [M+H] ⁺
133	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(4-methoxy-6-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		484
134	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-6-methylpyridin-2-yl)acrylic acid		454
135	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-3-methylpyridin-2-yl)acrylic acid		454
136	(E)-3-(4-((E)-2-(5-Chloro-6-methoxypyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		504
137	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(5-fluoro-6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid		488
138	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid		470
139	(E)-3-(4-((E)-1-(3-Fluoro-1 <i>H</i> -indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)but-1-en-1-yl)phenyl)acrylic acid		458
140	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)-6-methylpyridin-2-yl)acrylic acid		499

Example	Name	Structure	LCMS [M+H] ⁺
141	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(pyridin-2-yl)vinyl)phenyl)acrylic acid		440
142	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid		458
143	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		474
144	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid		454
145	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid		508
146	(E)-3-(4-((E)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		508
147	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(6-methoxypyridin-2-yl)vinyl)phenyl)acrylic acid		470
148	(E)-3-(4-((E)-1-(3-Cyano-1 <i>H</i> -indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid		444 [M-H] ⁻

Example	Name	Structure	LCMS [M+H] ⁺
149	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid		459
150	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,5-dimethylthiophen-3-yl)-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		473
151	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-1-(1 <i>H</i> -indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		438
152	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		477
153	(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		459
154	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid		443
155	(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		468
156	(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		466 [M-H] ⁻

Example	Name	Structure	LCMS [M+H] ⁺
157	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		460
158	(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(5-methoxy-3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid		470
159	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)pyrazin-2-yl)acrylic acid		441
160	(E)-3-(6-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)pyridin-3-yl)acrylic acid		440
161	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-3-fluoropyridin-2-yl)acrylic acid		458
162	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)pyrimidin-2-yl)acrylic acid		441
163	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1 <i>H</i> -indazol-4-yl)but-1-en-1-yl)phenyl)acrylic acid		465
164	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-6-methoxypyridin-2-yl)acrylic acid		470

Example	Name	Structure	LCMS [M+H] ⁺
165	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)-3-methoxypyridin-2-yl)acrylic acid		470
166	(E)-3-(3-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		473
167	(E)-3-(2-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		473
168	(E)-3-(5-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		492
169	(E)-3-(5-((Z)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		474
220	(E)-3-(4-((E)-2-Cyclobutyl-2-(2,4-dichlorophenyl)-1-(imidazo[1,2- <i>a</i>]pyridin-6-yl)vinyl)phenyl)acrylic acid		489
221	(E)-3-(4-((E)-2-Cyclobutyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)-1-(imidazo[1,2- <i>a</i>]pyridin-6-yl)vinyl)phenyl)acrylic acid		507
222	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1 <i>H</i> -indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid		502

Example	Name	Structure	LCMS [M+H] ⁺
223	(E)-3-(4-((E)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid		523
224	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(5-cyanoimidazo[1,2-a]pyridin-6-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		498
225	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		516
226	(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid		480
227	(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid		480
228	(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid		485
229	(E)-3-(4-((E)-2-Cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid		465
230	(E)-3-(4-((E)-2-(2-Chloro-4-ethoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		517

Example	Name	Structure	LCMS [M+H] ⁺
231	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)acrylic acid		523
232	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		502
233	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(hydroxymethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		502
234	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chlorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		472
235	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-3-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		490
236	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-5-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		490
237	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid		482
238	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid		452

Example	Name	Structure	LCMS [M+H] ⁺
239	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid		470
240	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid		482
241	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		556
242	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		531
243	(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		532
244	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		541
245	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid		484
246	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid		474

Example	Name	Structure	LCMS [M+H] ⁺
247	(E)-3-(4-((E)-2-(3-Cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		465
248	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-cyano-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid		496 [M-H] ⁻
249	(E)-3-(4-((E)-2-(5-Chloro-3-cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		499
250	(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		542
251	(E)-3-(4-((E)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		492
252	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-(trifluoromethyl)-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		539 [M-H] ⁻
253	(E)-3-(4-((Z)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid		510
254	(E)-3-(4-((Z)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid		526

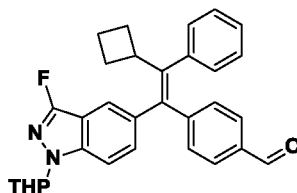
Example	Name	Structure	LCMS [M+H] ⁺
255	(E)-Ethyl 3-(4-((Z)-2-cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylate		554
256	(E)-3-(4-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid		521
257	(E)-3-(4-((E)-2-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		542
258	(E)-3-(4-((E)-2-(4,6-bis(Trifluoromethyl)pyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		576
259	(E)-3-(5-((Z)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		475
260	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)pyridin-2-yl)acrylic acid		509
261	(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		447
262	(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		448

Example	Name	Structure	LCMS [M+H] ⁺
263	(E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)but-1-en-1-yl)phenyl)acrylic acid		482
264	(E)-3-(4-((E)-2-(3,5-Dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid		482
265	(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-2-fluorophenyl)acrylic acid		457
266	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)but-2-enoic acid		453
267	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-2-methylacrylic acid		453
268	(E)-3-(5-((Z)-2-Cyclobutyl-2-(2,4-dichlorophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		508
269	(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)pyridin-2-yl)acrylic acid		526
270	(E)-3-(5-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		504

Example	Name	Structure	LCMS [M+H] ⁺
271	(E)-3-(4-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid		509
272	(E)-3-(5-((Z)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid		558
273	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		557
274	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid		540
275	(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid		541

Intermediate 56

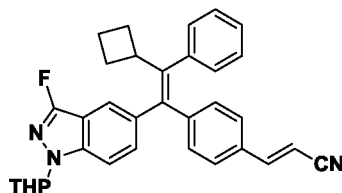
(E)-4-(2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)benzaldehyde



[00597] The title compound was prepared from Intermediate 14, (4-formylphenyl)boronic acid, and iodobenzene following General Procedure C. ¹H NMR (400 MHz, DMSO-d₆): δ 9.78 (s, 1H), 7.87 (dd, 1H), 7.60 (s, 1H), 7.53 (d, 2H), 7.37 (dd, 1H), 7.28-7.22 (m, 2H), 7.19-7.12 (m, 5H), 5.79 (m, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.40 (m, 1H), 2.35-2.20 (m, 1H), 2.06-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.67-1.50 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 397 [(M+H-THP)+H]⁺.

Intermediate 57

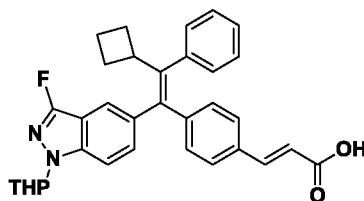
(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylonitrile



[00598] The title compound was prepared from Intermediate 56 and diethyl (cyanomethyl)phosphonate following General Procedure E. ^1H NMR (400 MHz, DMSO- d_6): δ 7.75 (dd, 1H), 7.57 (s, 1H), 7.43 (d, 1H), 7.33 (dd, 1H), 7.30-7.22 (m, 4H), 7.20-7.12 (m, 3H), 6.96 (d, 2H), 6.26 (d, 1H), 5.80 (m, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.38 (m, 1H), 2.31 (m, 1H), 2.06-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.67-1.50 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 504 (M+H) $^+$.

Intermediate 58

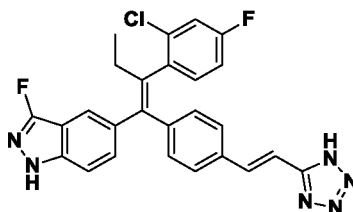
(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid



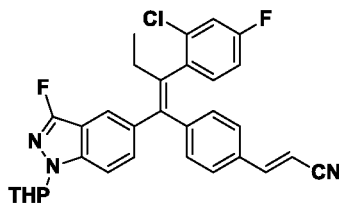
[00599] The title compound was prepared from Intermediate 14 following General Procedures C & G. LCMS: 523 (M+H) $^+$.

Example 170

5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)-3-fluoro-1H-indazole

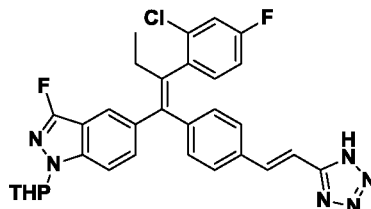


Step 1: (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylonitrile



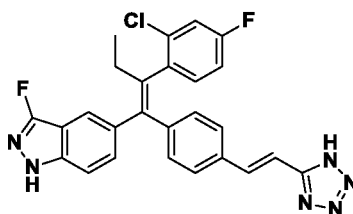
[00600] The title compound was prepared from Intermediate 16 following General Procedures D and E. ¹H NMR (400MHz, DMSO-d₆): δ 7.78 (d, 1H), 7.64-7.60 (br s, 1H), 7.49-7.43 (d, 1H), 7.41-7.32 (m, 5H), 7.17-7.11 (dt, 1H), 6.99 (d, 2H), 6.30 (d, 1H), 5.79 (d, 1H), 3.92-3.85 (m, 1H), 3.78-3.68 (m, 1H), 2.41-2.21 (m, 3H), 2.06-1.92 (m, 2H), 1.78-1.67 (m, 1H), 1.61-1.51 (m, 2H), 0.89 (t, 3H); LCMS: 446 [(M-THP+H)+H]⁺.

Step 2: 5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



[00601] A 40 mL vial equipped with a magnetic stir bar was charged with (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylonitrile (192 mg, 0.36 mmol), di-n-butyltin oxide (90 mg, 0.36 mmol), and anhydrous toluene (2 mL). This mixture was degassed with 3 vacuum/N₂ cycles, and trimethylsilylazide (481 μL, 3.6 mmol) was added. The resulting mixture was heated at 110 °C for 1 h. Upon completion of the reaction, the crude material was poured onto a silica gel column and eluted with 0-25% ethyl acetate/hexane and then 0-20% methanol in DCM to give the title compound (136 mg). ¹H NMR (400MHz, DMSO-d₆): δ 7.78 (d, 1H), 7.62 (br s, 1H), 7.49-7.34 (m, 6H), 7.21-7.12 (m, 2H), 6.99 (d, 2H), 5.80 (d, 1H), 3.92-3.85 (m, 1H), 3.75-3.68 (m, 1H), 2.40-2.22 (m, 3H), 2.05-1.92 (m, 2H), 1.80-1.67 (m, 1H), 1.60-1.51 (m, 2H), 0.91 (t, 3H); LCMS: 489 [(M-THP+H)+H]⁺.

Step 3: 5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)-3-fluoro-1H-indazole



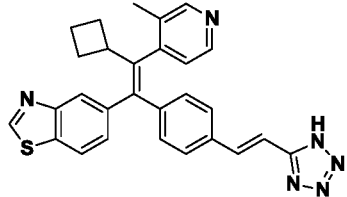
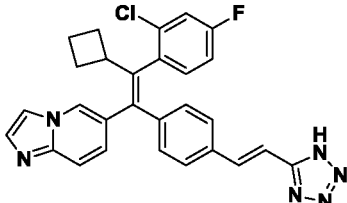
[00602] The title compound was prepared from 5-((E)-1-(4-((E)-2-(2H-tetrazol-5-yl)vinyl)phenyl)-2-phenylbut-1-en-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole following

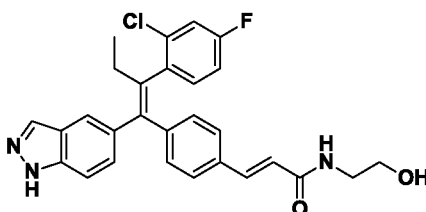
General Procedure F. ^1H NMR (400MHz, DMSO- d_6): δ 12.63 (s, 1H), 7.60 (s, 1H), 7.54-7.45 (m, 2H), 7.42 (d, 2H), 7.39-7.34 (m, 2H), 7.28 (dd, 1H), 7.20-7.12 (m, 2H), 7.00 (d, 2H), 2.39 (q, 2H), 0.90 (t, 3H); LCMS: 489 (M+H) $^+$.

[00603] The Examples in Table 12 were prepared following the procedures outlined for Example 170 (Step 3 optional).

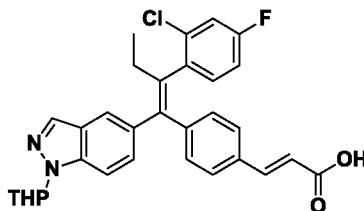
Table 12.

Example	Name	Structure	LCMS [M+H] $^+$
171	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)but-1-en-1-yl)-3-fluoro-1H-indazole		472
172	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)-3-fluoro-1H-indazole		498
173	4-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)-1H-indazole		497
174	5-((E)-1-(4-((E)-2-(1H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole		463
175	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)benzo[d]thiazole		514
176	5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)benzo[d]thiazole		497

Example	Name	Structure	LCMS [M+H] ⁺
177	5-((E)-1-(4-((E)-2-(2 <i>H</i> -Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)benzo[d]thiazole		477
178	6-((E)-1-(4-((E)-2-(2 <i>H</i> -Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)imidazo[1,2-a]pyridine		497

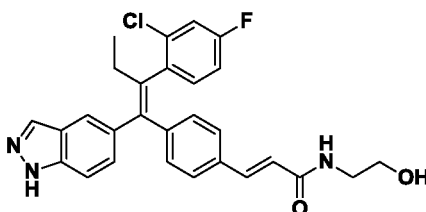
Example 179**(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)-N-(2-hydroxyethyl)acrylamide**

Step 1: (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid



[00604] The title compound was prepared from 5-bromoindazole following General Procedures A, B, D, E, and G. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.28 (s, 1H), 8.11 (s, 1H), 7.72 (d, 1H), 7.69 (s, 1H), 7.47-7.36 (m, 5H), 7.35-7.32 (m, 1H), 7.28-7.23 (m, 1H), 6.95 (d, 2H), 6.40 (d, 1H), 5.86 (dd, 1H), 3.91-3.88 (m, 1H), 3.74-3.71 (m, 1H), 2.44-2.33 (m, 3H), 2.06-1.97 (m, 2H), 1.74 (m, 1H), 1.60-1.59 (m, 2H), 0.90 (t, 3H). LCMS: 447 [(M-THP+H)+H]⁺.

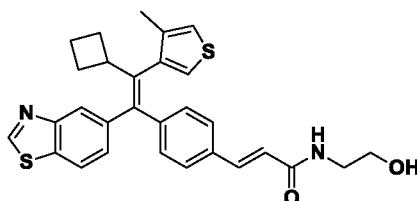
Step 2: (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)-N-(2-hydroxyethyl)acrylamide



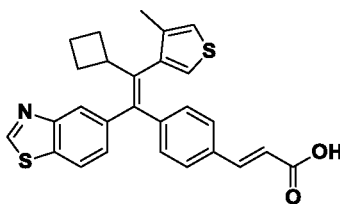
[00605] A 20 mL vial equipped with a magnetic stir bar was charged with (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid (0.20 g, 0.38 mmol), ethanolamine (45 μ L, 0.75 mmol), triethylamine (105 μ L, 0.75 mmol), and DMF (2.0 mL). HATU (215 mg, 0.56 mmol) was added, and the resulting mixture was stirred at room temperature for 2.5 h and then directly purified by reverse-phase HPLC. A solution of this material and 1.25N HCl in EtOH (2 mL) was heated at 80 °C for 30 min, cooled to room temperature, diluted with water, and then extracted with ethyl acetate. The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified on a silica gel column eluted with 100% ethyl acetate in hexanes affording the title compound as white solid (36 mg) ^1H NMR (400 MHz, DMSO- d_6): δ 13.10 (s, 1H), 8.09 (s, 1H), 8.00 (t, 1H), 7.68 (s, 1H), 7.55 (d, 1H), 7.37-7.32 (m, 2H), 7.25-7.18 (m, 4H), 7.16-7.10 (dt, 1H), 6.94 (d, 2H), 6.50 (d, 1H), 4.68 (t, 1H), 3.41 (q, 2H), 3.18 (q, 2H), 2.38 (q, 2H), 0.90 (t, 3H); LCMS: 490 (M+H) $^+$.

Example 180

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide

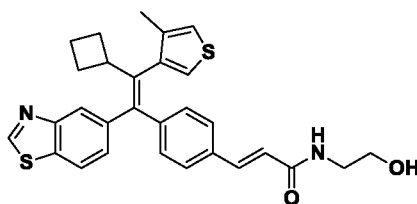


Step 1: (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid



[00606] The title compound was prepared from Intermediate 15 following General Procedures D, E, & G. ^1H NMR (400 MHz, DMSO- d_6): δ 12.25 (s, 1H), 9.43 (s, 1H), 8.18 (d, 1H), 7.89 (s, 1H), 7.42 (d, 1H), 7.36-7.28 (m, 4H), 7.04 (s, 1H), 6.96 (d, 2H), 6.35 (d, 1H), 3.37 (m, 1H), 2.00 (m, 1H), 1.97 (s, 3H), 1.81-1.75 (m, 2H), 1.68-1.56 (m, 2H), 1.41 (m, 1H); LCMS: 458 (M+H) $^+$.

Step 2: (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide



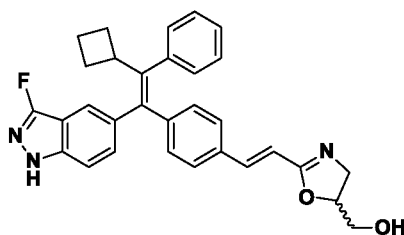
[00607] A mixture of (E)-3-(4-((E)-1-(benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid (197 mg, 0.43 mmol), ethanolamine (51 μ L, 0.86 mmol), HATU (245 mg, 0.64 mmol), triethylamine (119 μ L, 0.86 mmol), and DMF (4.3 mL) was stirred at room temperature overnight. The reaction mixture was directly purified by reverse-phase HPLC to afford 113 mg of (E)-3-(4-((E)-1-(benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide as a pale yellow solid. ^1H NMR (400 MHz, DMSO- d_6): δ 9.43 (s, 1H), 8.18 (d, 1H), 8.01 (t, 1H), 7.89 (s, 1H), 7.31-7.21 (m, 5H), 7.04 (s, 1H), 6.95 (d, 2H), 6.51 (d, 1H), 3.43-3.32 (m, 3H), 3.20 (q, 2H), 2.03 (m, 1H), 1.96 (s, 3H), 1.82-1.75 (m, 2H), 1.68-1.56 (m, 2H), 1.40 (m, 1H); LCMS: 501 ($\text{M}+\text{H}$) $^+$.

[00608] The Examples in Table 13 were prepared following the procedures outlined for Examples 179 & 180.

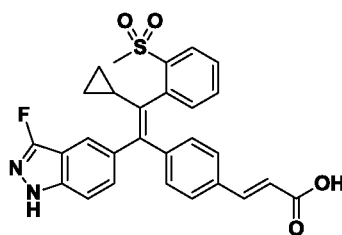
Table 13.

Example	Name	Structure	LCMS [$\text{M}+\text{H}$] $^+$
181	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide		502
182	(E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide		465
183	(E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-4-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide		464

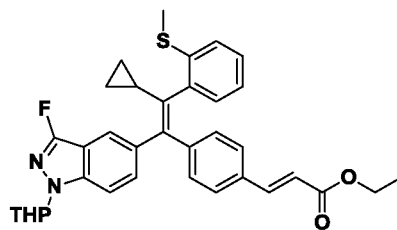
Example	Name	Structure	LCMS [M+H] ⁺
184	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)phenyl)-N-methylacrylamid		477
185	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1 <i>H</i> -indazol-5-yl)but-1-en-1-yl)phenyl)-N-(thiazol-2-yl)acrylamide		529
186	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)-N-(thiazol-2-yl)acrylamide		573
187	(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(imidazo[1,2-a]pyridin-6-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide		516
188	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,3-dihydroxypropyl)acrylamide		512
189	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)-N-(1,3-dihydroxypropan-2-yl)acrylamide		512
190	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide		452
191	(E)-N-(2-Chloroethyl)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylamide		500

Example 192**(2-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-4,5-dihydrooxazol-5-yl)methanol**

[00609] The title compound was isolated during the purification of Example 188. LCMS: 494 (M+H)⁺.

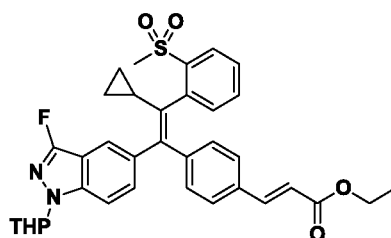
Example 193**(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid**

Step 1: ((E)-Ethyl 3-(4-((E)-2-cyclopropyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-(methylthio)phenyl)vinyl)phenyl)acrylate



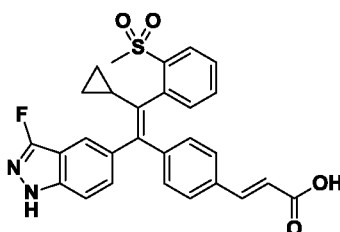
[00610] The title compound was prepared from Intermediate 31, 2-iodothioanisole, and (E)-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)boronic acid following General Procedure C. ¹H NMR (400 MHz, DMSO-d₆): δ 7.78 (m, 1H), 7.69 (m, 1H), 7.48-7.43 (m, 2H), 7.34 (d, 2H), 7.18 (m, 1H), 7.11 (m, 1H), 7.08-6.98 (m, 4H), 6.44 (d, 1H), 5.78 (m, 1H), 4.15 (q, 2H), 3.88 (m, 1H), 3.71 (m, 1H), 2.39 (s, 3H), 2.05-1.90 (m, 2H), 1.80-1.60 (m, 2H), 1.58-1.50 (m, 2H), 1.25 (m, 1H), 1.20 (t, 3H), 0.60 (m, 2H), 0.31 (m, 1H), 0.11 (m, 1H); LCMS: 583 (M+H)⁺.

Step 2: (E)-Ethyl 3-(4-((E)-2-cyclopropyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylate



[00611] Potassium peroxymonosulfate (650 mg, 1.05 mmol) was added to a slurry of ((E)-ethyl 3-(4-((E)-2-cyclopropyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-(methylthio)phenyl)vinyl)phenyl)acrylate (115 mg, 0.197 mmol) in THF:MeOH:H₂O (1:1:1, 3 mL) at room temperature, and the reaction was stirred overnight. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (2x20 mL). The organic phase was dried (Na₂SO₄), concentrated under reduced pressure, and purified on a silica gel column to give the desired compound (106 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 7.78 (d, 1H), 7.82-7.73 (m, 2H), 7.60 (m, 1H), 7.53-7.43 (m, 3H), 7.42-7.32 (m, 3H), 6.98 (d, 2H), 6.44 (d, 1H), 5.79 (m, 1H), 4.13 (q, 2H), 3.88 (m, 1H), 3.71 (m, 1H), 2.88 (s, 3H), 2.25 (m, 1H), 2.10-1.90 (m, 2H), 1.81-1.65 (m, 2H), 1.60-1.51 (m, 2H), 1.25 (t, 3H), 0.65-0.52 (m, 2H), 0.25 (m, 1H), 0.13 (m, 1H); LCMS: 615 (M+H)⁺.

Step 3: (E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid



[00612] The title compound was prepared from ((E)-ethyl 3-(4-((E)-2-cyclopropyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylate following General Procedures F and G. ¹H NMR (400 MHz, DMSO-d₆): δ 12.59 (s, 1H), 7.87 (dd, 1H), 7.74 (s, 1H), 7.60 (m, 1H), 7.55-7.47 (m, 2H), 7.46-7.33 (m, 5H), 6.99 (d, 2H), 6.34 (d, 1H), 2.89 (s, 3H), 1.69 (m, 1H), 0.70-0.52 (m, 2H), 0.30-0.20 (m, 1H), 0.15-0.08 (m, 1H); LCMS: 503 (M+H)⁺.

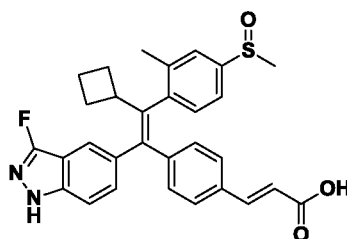
[00613] The Examples in Table 14 were prepared following the procedures outlined for Example 193.

Table 14.

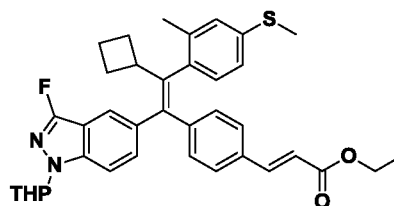
Example	Name	Structure	LCMS [M+H] ⁺
194	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid		517
195	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid		531
196	(E)-3-(4-((E)-2-(2-Chloro-4-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1 <i>H</i> -indazol-5-yl)vinyl)phenyl)acrylic acid		551
197	(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid		516

Example 198

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-(2-methyl-4-(methylsulfinyl)phenyl)vinyl)phenyl)acrylic acid

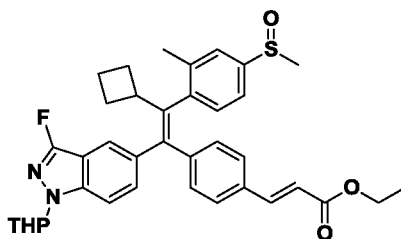


Step 1: (E)-Ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-(2-methyl-4-(methylthio)phenyl)vinyl)phenyl)acrylate



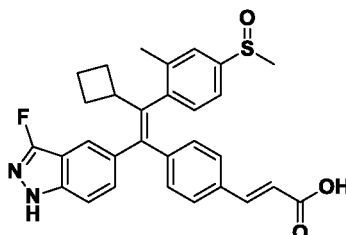
[00614] The title compound was an intermediate in the preparation of Example 72. ¹H NMR (400MHz, DMSO-d₆): δ 7.76 (d, 1H), 7.56 (d, 1H), 7.45 (d, 1H), 7.39-7.32 (m, 3H), 7.11 (d, 1H), 7.03 (dd, 1H), 6.99-6.94 (m, 3H), 6.45 (d, 1H), 5.80 (d, 1H), 4.13 (q, 2H), 3.92-3.85 (m, 1H), 3.77-3.69 (m, 1H), 3.40-3.30 (m, 1H), 2.42 (s, 3H), 2.34-2.20 (m, 1H), 2.12 (s, 3H), 2.06-1.91 (m, 2H), 1.89-1.83 (m, 1H), 1.83-1.66 (m, 3H), 1.66-1.50 (m, 4H), 1.39-1.30 (m, 1H), 1.21 (t, 3H). LCMS: 611(M+H)⁺.

Step 2: (E)-Ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfinyl)phenyl)vinyl)phenyl)acrylate



[00615] Tetrahydrofuran (1.1 mL) and (E)-ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-methyl-4-(methylthio)phenyl)vinyl)phenyl)acrylate (190 mg, 0.31 mmol) were added to a solution of sodium periodate (103 mg, 0.48 mmol) in water (0.55 mL) at room temperature. The reaction was stirred at rt for 21.5 h and then heated at 40 °C for 5.5 h. Additional sodium periodate (67 mg, 0.31 mmol) was added, and the reaction was heated at 40 °C for 3 h, allowed to cool to rt, and then diluted with EtOAc. The organic layer was washed with water (30 mL) and then brine (30 mL). Each aqueous layer was back extracted with EtOAc (30 mL), and the combined organic extracts were dried (MgSO₄), filtered, concentrated, and purified by silica gel chromatography (20%-70% EtOAc in hexanes) to give (E)-ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfinyl)phenyl)vinyl)phenyl)acrylate as a white foam (85 mg). ¹H NMR (400MHz, DMSO-d₆): δ 7.78 (d, 1H), 7.61 (d, 1H), 7.51-7.35 (m, 7H), 6.95 (d, 2H), 6.44 (d, 1H), 5.81 (d, 1H), 4.12 (q, 2H), 3.92-3.86 (m, 1H), 3.78-3.70 (m, 1H), 3.45-3.36 (m, 1H), 2.71 (s, 3H), 2.34-2.20 (m, 4H), 2.06-1.93 (m, 2H), 1.91-1.68 (m, 4H), 1.65-1.52 (m, 4H), 1.42-1.32 (m, 1H), 1.21 (t, 3H).

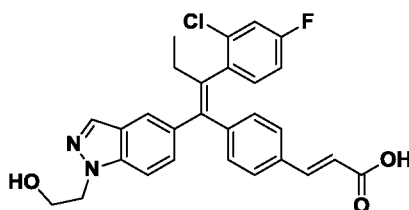
Step 3: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfinyl)phenyl)vinyl)phenyl)acrylic acid



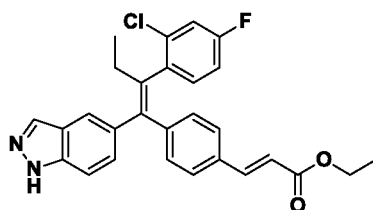
[00616] The title compound was prepared from (E)-ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfinyl)phenyl)vinyl)phenyl)acrylate following General Procedures F & G. ¹H NMR (400MHz, DMSO-d₆): δ 12.60 (s, 1H), 7.53 (s, 1H), 7.49 (d, 1H), 7.39 (d, 1H), 7.34 (d, 2H), 7.24 (dd, 1H), 7.10 (d, 1H), 7.03 (d, 1H), 6.99-6.93 (m, 3H), 6.35 (d, 1H), 3.37 (m, 1H), 2.42 (s, 3H), 2.12 (s, 3H), 1.94-1.68 (m, 3H), 1.65-1.53 (m, 2H), 1.42-1.30 (m, 1H). LCMS: 515 (M+H)⁺.

Example 199

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid

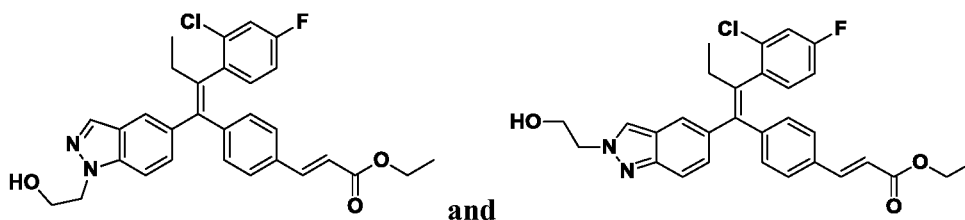


Step 1: (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate



[00617] The title compound was prepared from 5-bromoindazole following General Procedures A, B, D, E, & F. LCMS: 475 (M+H)⁺.

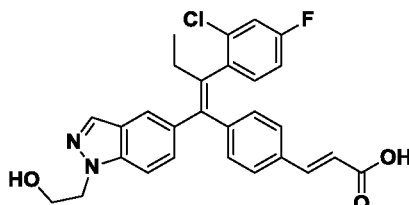
Step 2: (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate and (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(2-(2-hydroxyethyl)-2H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate



[00618] A mixture of (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate (494 mg, 1.04 mmol), ethylene carbonate (457 mg, 5.2 mmol), and cesium carbonate (678 mg, 2.1 mmol) in DMF (7 mL) was heated at 90°C for 1h, cooled to room temperature, and then diluted with EtOAc and H₂O. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified on silica gel

column to afford 280 mg of (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate (least polar compound); LCMS: 519 (M+H)⁺ and 138 mg of (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(2-(2-hydroxyethyl)-2*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate (more polar compound); LCMS: 519 (M+H)⁺.

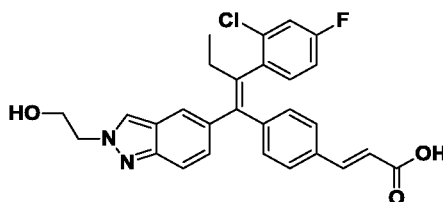
Step 3: (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid



[00619] The title compound was prepared from (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1-(2-hydroxyethyl)-1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate following General Procedure G. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.06 (s, 1H), 7.77-7.65 (m, 2H), 7.37-7.28 (m, 5H), 7.20 (d, 1H), 7.14 (td, 1H), 6.94 (d, 2H), 6.35 (d, 1H), 4.43 (t, 2H), 3.81 (t, 2H), 2.48 (q, 2H), 0.91 (t, 3H); LCMS: 491 (M+H)⁺.

Example 200

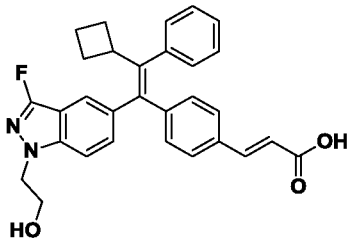
(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(2-(2-hydroxyethyl)-2*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid

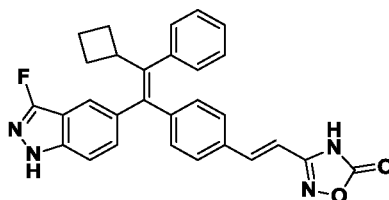


[00620] The title compound was prepared from (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(2-(2-hydroxyethyl)-2*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate following General Procedure G. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.39 (s, 1H), 7.64 (s, 1H), 7.59 (d, 1H), 7.42-7.31 (m, 5H), 7.12 (td, 1H), 7.01 (d, 1H), 6.96 (d, 2H), 6.35 (d, 1H), 4.45 (t, 2H), 3.87 (t, 2H), 2.44 (q, 2H), 0.90 (t, 3H); LCMS: 491 (M+H)⁺.

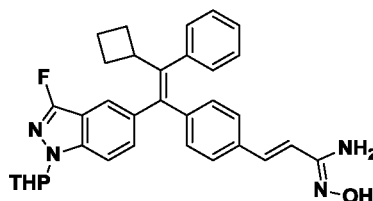
[00621] The Example in Table 15 was prepared from Intermediate 14 following General Procedures C & F then Steps 2 & 3 of Example 199.

Table 15.

Example	Name	Structure	LCMS [M+H] ⁺
201	(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(2-hydroxyethyl)-1 <i>H</i> -indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid		483

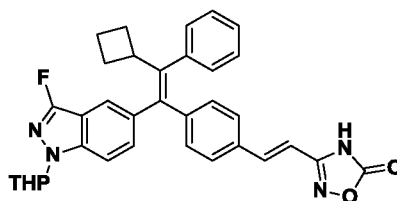
Example 202**3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4*H*)-one**

Step 1: (1*Z*,2*E*)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)-*N*'-hydroxyacrylimidamide



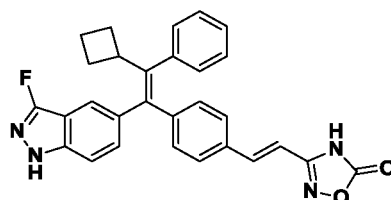
[00622] A mixture of Intermediate 57 (2.62 g, 5.21 mmol) and hydroxylamine (0.52 mL, 7.9 mmol, 50% wt. in water) in ethanol (25 mL) was heated at reflux for 4 h. The ethanol was removed under reduced pressure, and the residue was purified on a silica gel column to give the title compound (1.83 g) as a pale yellow foam. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.64 (s, 1H), 7.75 (dd, 1H), 7.55 (s, 1H), 7.33 (dd, 1H), 7.29-7.22 (m, 2H), 7.20-7.05 (m, 5H), 6.89-6.81 (m, 3H), 6.20 (d, 1H), 5.77 (m, 1H), 5.47 (s, 2H), 3.89 (m, 1H), 3.72 (m, 1H), 3.34 (m, 1H), 2.25 (m, 1H), 2.06-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.67-1.50 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 537 (M+H)⁺.

Step 2: 3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4*H*)-one



[00623] To a mixture of (1Z,2E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N'-hydroxyacrylimidamide (975 mg, 1.82 mmol) and carbonyldiimidazole (445 mg, 2.74 mmol) in anhydrous THF (17 mL), DBU (0.82 mL, 5.5 mmol) was added. The resulting solution was stirred at room temperature overnight, diluted with ethyl acetate (100 mL), and washed (2 x 50 mL H₂O, 50 mL brine). The aqueous was back extracted with ethyl acetate (50 mL). The combined organic phases were dried (Na₂SO₄), concentrated under reduced pressure, and purified on a silica gel column to give the title compound (1.00 g) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.60 (s, 1H), 7.77 (dd, 1H), 7.57 (s, 1H), 7.36 (dd, 1H), 7.29-7.22 (m, 4H), 7.22-7.12 (m, 4H), 6.97 (d, 2H), 6.77 (d, 1H), 5.80 (m, 1H), 3.88 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.28 (m, 1H), 2.08-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.67-1.52 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 563 (M+H)⁺.

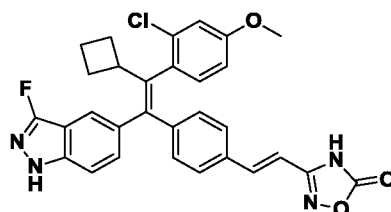
Step 3: 3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one



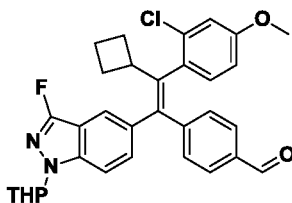
[00624] The title compound was prepared from 3-((E)-4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one following General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.60 (s, 1H), 7.54 (s, 1H), 7.49 (dd, 1H), 7.33-7.23 (m, 5H), 7.18-7.12 (m, 4H), 6.96 (d, 2H), 6.73 (d, 1H), 3.40 (m, 1H), 1.87-1.75 (m, 4H), 1.67-1.54 (m, 1H), 1.40-1.32 (m, 1H); LCMS: 477 (M-H)⁻.

Example 276

3-((E)-4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one

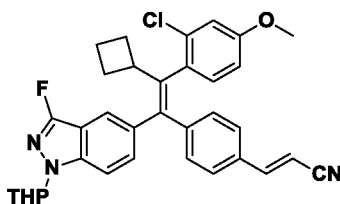


Step 1: (E)-4-(2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)benzaldehyde



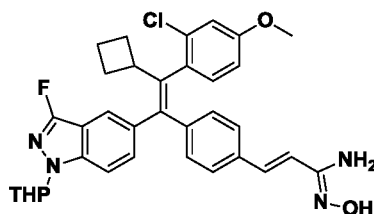
[00625] The title compound was prepared from Intermediate 14, 1-bromo-2-chloro-4-methoxybenzene and 4-iodobenzaldehyde following General Procedure D. ¹H NMR (400MHz, DMSO-d₆): δ 9.80 (s, 1H), 7.78 (d, 1H), 7.60-7.56 (m, 3H), 7.39-7.7.36 (m, 1H), 7.26-7.19 (m, 3H), 6.99 (d, 1H), 6.86 (dd, 1H), 5.80 (d, 1H), 3.92-3.85 (m, 1H), 3.76-3.68 (m, 4H), 3.42-3.33 (m, 1H), 2.32-2.21 (m, 1H), 2.07-1.91 (m, 3H), 1.90-1.75 (m, 3H), 1.74-1.62 (m, 2H), 1.61-1.52 (m, 2H), 1.43-1.33 (m, 1H); LCMS: 545 (M+H)⁺.

Step 2: (E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)acrylonitrile



[00626] The title compound was prepared from (E)-4-(2-(2-chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)benzaldehyde and diethyl (cyanomethyl)phosphonate following General Procedure E. ¹H NMR (400 MHz, DMSO-d₆): δ 7.78 (d, 1H), 7.54 (m, 1H), 7.45 (d, 1H), 7.36-7.31 (m, 3H), 7.22-7.18 (dd, 1H), 7.05-7.01 (d, 2H), 6.97-6.94 (m, 1H), 6.88-6.83 (dd, 1H), 6.29 (d, 1H), 5.80 (d, 1H), 3.92-3.85 (m, 1H), 3.76-3.68 (m, 4H), 3.39-3.33 (m, 1H), 2.34-2.21 (m, 1H), 2.09-1.91 (m, 3H), 1.90-1.62 (m, 5H), 1.61-1.52 (m, 2H), 1.43-1.33 (m, 1H); LCMS: 568 (M+H)⁺.

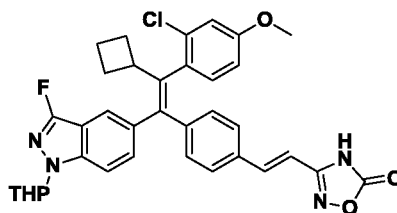
Step 3: (1Z,2E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)-N'-hydroxyacrylimidamide



[00627] A mixture of (E)-3-(4-((E)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)acrylonitrile (1.35 g, 2.38 mmol) and hydroxylamine (0.10 mL, 3.56 mmol, 50% wt. in water) in ethanol (9.5 mL) was heated at reflux for 1.5 h. The ethanol was removed under reduced pressure, and the residue was purified on a silica gel

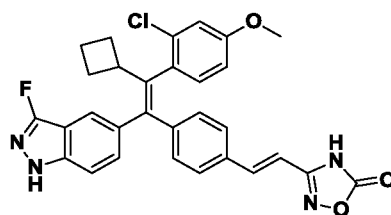
column to give the title compound (0.95 g) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.66 (s, 1H), 7.76 (d, 1H), 7.54 (m, 1H), 7.39 (m, 1H), 7.22-7.12 (m, 3H), 6.98-6.92 (m, 3H), 6.91-6.82 (m, 2H), 6.23 (d, 1H), 5.80 (d, 1H), 5.48 (s, 2H), 3.92-3.85 (m, 1H), 3.76-3.68 (m, 4H), 3.39-3.33 (m, 1H), 2.34-2.21 (m, 1H), 2.09-1.91 (m, 3H), 1.90-1.62 (m, 5H), 1.61-1.52 (m, 2H), 1.43-1.33 (m, 1H); LCMS: 601 ($\text{M}+\text{H}$) $^+$.

Step 4: 3-((E)-4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one



[00628] 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.95 mL, 6.32 mmol) was added dropwise to a solution of (1Z,2E)-3-(4-((E)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)phenyl)-N'-hydroxyacrylimidamide (950 mg, 1.58 mmol) and carbonyldiimidazole (513 mg, 3.16 mmol) in anhydrous THF (8 mL). The resulting solution was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with H_2O , washed with brine, dried over (Na_2SO_4), concentrated under reduced pressure, and purified on a silica gel column to give the title compound (855 mg) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H), 7.78 (d, 1H), 7.54 (m, 1H), 7.36-7.30 (m, 3H), 7.24-7.17 (m, 2H), 7.02 (d, 2H), 6.96 (d, 1H), 6.86 (dd, 1H), 6.80 (d, 1H), 5.80 (d, 1H), 3.92-3.85 (m, 1H), 3.78-3.68 (m, 4H), 3.39-3.33 (m, 1H), 2.34-2.21 (m, 1H), 2.08-1.92 (m, 2H), 1.90-1.62 (m, 6H), 1.61-1.52 (m, 2H), 1.43-1.33 (m, 1H); LCMS: 627 ($\text{M}+\text{H}$) $^+$.

Step 5: 3-((E)-4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one



[00629] The title compound was prepared from 3-((E)-4-((E)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one following General Procedure F. ^1H NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H), 7.52 (s, 1H), 7.49 (m, 1H), 7.36-7.32 (d, 2H), 7.26-7.17 (m, 3H), 7.02 (d, 2H), 6.95 (d, 1H), 6.86 (dd, 1H), 6.81 (d, 1H), 3.72 (s, 3H), 3.39-3.34 (m, 1H), 1.92-1.74 (m, 3H), 1.73-1.65 (m, 1H), 1.64-1.55 (m, 1H), 1.42-1.33 (m, 1H); LCMS: 543 ($\text{M}+\text{H}$) $^+$.

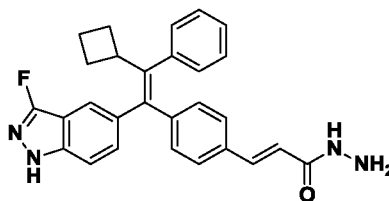
The Examples in Table 16 were prepared following the procedures outlined for Example 202 and Example 276.

Table 16.

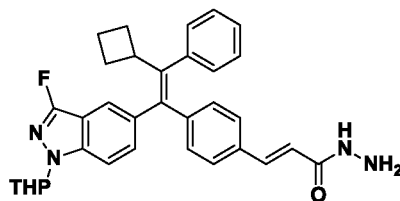
Example	Name	Structure	LCMS [M+H] ⁺
277	3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one		581
278	3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one		542
279	3-((E)-4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one		582
280	2-((E)-1-Cyclobutyl-2-(3-fluoro-1H-indazol-5-yl)-2-(4-((E)-2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)vinyl)phenyl)vinyl)-5-(trifluoromethyl)benzonitrile		572

Example 203

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylohydrazide

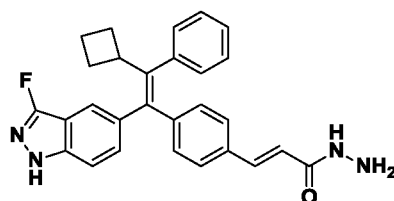


Step 1: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylohydrazide



[00630] To a solution of Intermediate 58 (160mg, 0.31 mmol) and HOBt (50 mg, 0.37 mmol) in acetonitrile (3 mL), EDCI (72 mg, 0.38 mmol) was added. The reaction mixture was stirred at room temperature for 50 min and cooled to 0°C. Hydrazine (20 uL, 0.64 mmol) was added, and the reaction mixture was stirred for additional 1h. The reaction was diluted with ethyl acetate (20 mL), washed (20 mL H₂O, 20 mL brine), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified on a silica gel column to give the title compound. LCMS: 537 (M+H)⁺.

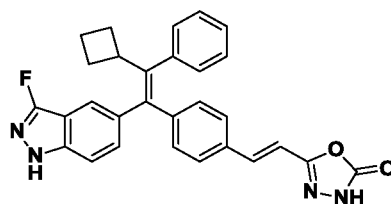
Step 2: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylohydrazide



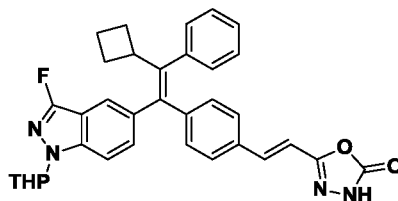
[00631] The title compound was prepared from (E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylohydrazide following General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.62 (s, 1H), 10.82 (s, 1H), 9.90 (br s, 1H), 7.54 (s, 1H), 7.49 (dd, 1H), 7.44 (d, 1H), 7.31-7.23 (m, 5H), 7.18-7.12 (m, 3H), 6.98 (d, 2H), 6.47 (d, 1H), 3.39 (m, 1H), 1.88-1.75 (m, 4H), 1.67-1.54 (m, 1H), 1.40-1.31 (m, 1H); LCMS: 453 (M+H)⁺.

Example 204

3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one

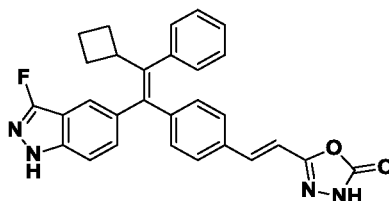


Step 1: 5-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,3,4-oxadiazol-2(3H)-one

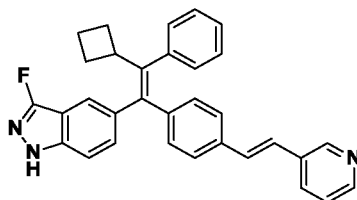
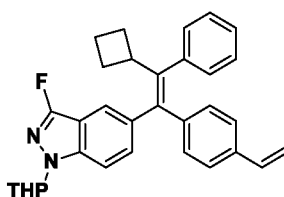


[00632] To a solution of Intermediate 58 (200mg, 0.38 mmol) and HOBt (63 mg, 0.47 mmol) in acetonitrile (5 mL), EDCI (89 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 2h and cooled to 0°C. Hydrazine (18 uL, 0.58 mmol) was added, and the reaction mixture was stirred for additional 1h. The reaction was diluted with H₂O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic phase was washed (20 mL H₂O, 20 mL brine), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was dissolved in THF (3 mL), and carbonyldiimidazole (62 mg, 0.38 mmol) and triethylamine (54 uL, 0.39 mmol) were added. The mixture was stirred at room temperature overnight, diluted with ethyl acetate (20 mL), washed (20 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified on a silica gel column to give the title compound (100 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 12.42 (s, 1H), 7.75 (dd, 1H), 7.58 (s, 1H), 7.38-7.32 (m, 3H), 7.29-7.22 (m, 2H), 7.19-7.07 (m, 4H), 6.93 (m, 2H), 6.71 (d, 1H), 5.80 (m, 1H), 3.89 (m, 1H), 3.73 (m, 1H), 3.38 (m, 1H), 2.30-2.20 (m, 1H), 2.08-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.65-1.52 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 563 (M+H)⁺.

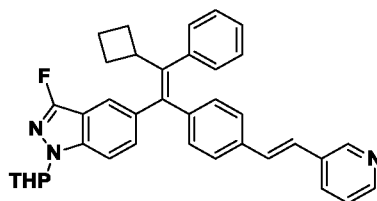
Step 2: 3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one



[00633] The title compound was prepared from 5-((E)-4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,3,4-oxadiazol-2(3H)-one following General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.59 (s, 1H), 12.42 (s, 1H), 7.56 (s, 1H), 7.48 (dd, 1H), 7.33 (d, 2H), 7.28-7.22 (m, 3H), 7.18-7.07 (m, 4H), 6.93 (d, 2H), 6.74 (d, 1H), 3.39 (m, 1H), 1.88-1.72 (m, 4H), 1.63-1.56 (m, 1H), 1.40-1.32 (m, 1H); LCMS: 479 (M+H)⁺.

Example 205**5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-3-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole****Step 1: (E)-5-(2-Cyclobutyl-2-phenyl-1-(4-vinylphenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole**

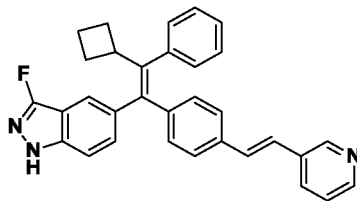
[00634] Potassium *tert*-butoxide (220 mg, 1.96 mmol) was added to a solution of methyltriphenylphosphonium bromide (780 mg, 1.93 mmol), and the mixture was stirred at room temperature for 20 min. (E)-4-(2-Cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylvinyl)benzaldehyde (599 mg, 1.25 mmol, Intermediate 56) in THF (5 mL) was added to the reaction, and the mixture was stirred for additional 2 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed (2 x 50 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified on a silica gel column to give the title compound (520 mg) as a white foam. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.74 (dd, 1H), 7.54 (s, 1H), 7.33 (dd, 1H), 7.28-7.23 (m, 2H), 7.18-7.12 (m, 3H), 7.07 (d, 2H), 6.87 (d, 2H), 6.51 (dd, 1H), 5.79 (m, 1H), 5.64 (d, 1H), 5.12 (d, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.40 (m, 1H), 2.35-2.20 (m, 1H), 2.06-1.90 (m, 2H), 1.90-1.70 (m, 5H), 1.67-1.50 (m, 3H), 1.40-1.30 (m, 1H); LCMS 479 (M+H)⁺.

Step 2: 5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-3-yl)vinyl)phenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00635] A mixture of (E)-5-(2-cyclobutyl-2-phenyl-1-(4-vinylphenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (79 mg, 0.17 mmol), 3-iodopyridine (52 mg, 0.25 mmol), palladium acetate (4 mg, 0.18 mmol), Trixiephos (7 mg, 0.17 mmol), and diethylisopropylamine (50 uL, 0.32 mmol) in acetonitrile (2 mL) was degassed by bubbling nitrogen for 10 min and then heated at 80 °C overnight. The reaction mixture was diluted with ethyl acetate (20 mL), washed (2 x 20 mL

H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified on a silica gel column to give the title compound. LCMS: 556 (M+H)⁺.

Step 3: 5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-3-yl)vinyl)phenyl)vinyl)-3-fluoro-1H-indazole



[00636] The title compound was prepared from 5-((E)-2-cyclobutyl-2-phenyl-1-(4-((E)-2-(pyridin-3-yl)vinyl)phenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole following General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 8.81 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.66 (dd, 1H), 7.53 (s, 1H), 7.50 (dd, 1H), 7.33-7.21 (m, 6H), 7.19-7.10 (m, 4H), 6.95 (d, 2H), 3.41 (m, 1H), 1.90-1.73 (m, 4H), 1.70-1.56 (m, 1H), 1.40-1.32 (m, 1H); LCMS: 472 (M+H)⁺.

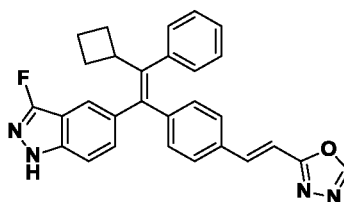
[00637] The Examples in Table 17 were prepared from THP-protected iodo-pyrazoles following the procedures outlined for Example 205.

Table 17.

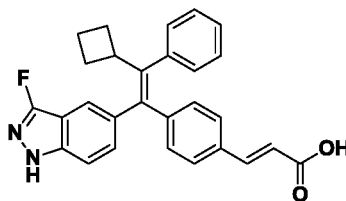
Example	Name	Structure	LCMS [M+H] ⁺
206	5-((E)-1-(4-((E)-2-(1H-Pyrazol-4-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole		461
207	5-((E)-1-(4-((E)-2-(1H-Pyrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole		461

Example 208

2-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,3,4-oxadiazole

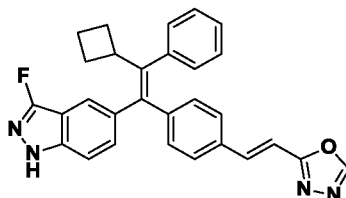


Step 1: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid



[00638] The title compound was prepared from Intermediate 14 following General Procedures C, F & G. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.59 (s, 1H), 12.26 (s, 1H), 7.55 (s, 1H), 7.50 (dd, 1H), 7.38 (d, 1H), 7.31 (d, 2H), 7.28-7.24 (m, 3H), 7.19-7.06 (m, 3H), 6.95 (d, 2H), 6.34 (d, 1H), 3.44-3.38 (m, 1H), 1.87-1.75 (m, 4H), 1.63-1.56 (m, 1H), 1.42-1.33 (m, 1H); LCMS: 439 (M+H)⁺.

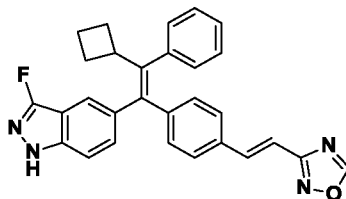
Step 2: 2-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)styryl)-1,3,4-oxadiazole



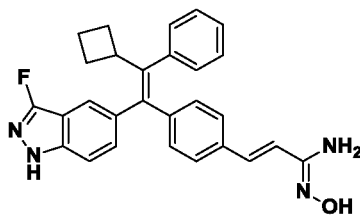
[00639] To a solution of (E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid (25 mg, 0.06 mmol) and formohydrazide (4 mg, 0.07 mmol) in ethyl acetate (1 mL), triethylamine (40 uL, 0.29 mmol) was added followed by propylphosphonic anhydride (50% in ethyl acetate, 50 uL, 0.08 mmol). The reaction mixture was heated at 80 °C overnight, concentrated under reduced pressure, and purified on a silica gel column to yield the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.58 (s, 1H), 9.16 (s, 1H), 7.75 (s, 1H), 7.48 (dd, 1H), 7.43-7.38 (m, 3H), 7.28-7.22 (m, 3H), 7.19-7.11 (m, 4H), 6.97 (d, 2H), 3.41 (m, 1H), 1.90-1.73 (m, 4H), 1.70-1.56 (m, 1H), 1.40-1.30 (m, 1H); LCMS: 463 (M+H)⁺.

Example 209

3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazole

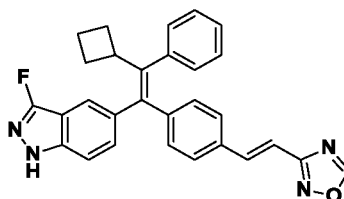


Step 1: (1Z,2E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)-N'-hydroxyacrylimidamide



[00640] A solution of (1Z,2E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)-N'-hydroxyacrylimidamide (160 mg, 0.298 mmol, Example 202, Step 1) in 4M HCl in dioxane (3 mL) was heated at 60 °C for 2 h. Additional 4M HCl in dioxane (2 mL) was added, and the mixture was heated at 60 °C overnight. The reaction mixture was diluted with ethyl acetate (20 mL), washed (2 x 10 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (130 mg). LCMS: 453 (M+H)⁺.

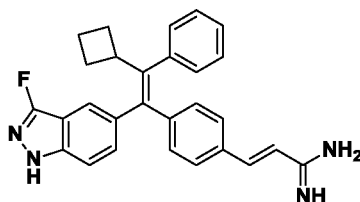
Step 2: 3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazole



[00641] To a solution of (1Z,2E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)-N'-hydroxyacrylimidamide (50 mg, 0.11 mmol) triethylamine (77 uL, 0.55 mmol), and formic acid (7 uL, 0.19 mmol) in ethyl acetate (3 mL), propylphosphonic anhydride (50% in ethyl acetate, 110 uL, 0.18 mmol) was added. The reaction mixture was heated at 80°C overnight, diluted with ethyl acetate (30 mL), washed (2x10 mL H₂O), and concentrated under reduced pressure. The residue was purified on a silica gel column to yield the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.58 (s, 1H), 9.51 (d, 1H), 7.57 (s, 1H), 7.53-7.46 (m, 2H), 7.38 (d, 2H), 7.28-7.23 (m, 3H), 7.18-7.10 (m, 4H), 6.97 (d, 2H), 3.43 (m, 1H), 1.90-1.73 (m, 4H), 1.70-1.58 (m, 1H), 1.40-1.32 (m, 1H); LCMS: 463 (M+H)⁺.

Example 210

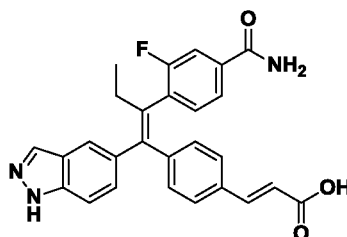
(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylvinyl)phenyl)acrylimidamide



[00642] Hydrogen chloride gas was bubbled through a solution of Intermediate 57 (97 mg, 0.19 mmol) and 20% ethanol in toluene (2.5 mL) for 1 h. The reaction mixture was kept at 0 °C overnight, concentrated under reduced pressure, and redissolved in ethanol (2 mL). Ammonia (7N in methanol) was added to the reaction at 0 °C, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by reverse-phase HPLC to give the title compound. ¹H NMR (400 MHz, DMSO-d₆, TFA salt): δ 12.63 (s, 1H), 8.92 (s, 2H), 8.60 (s, 2H), 7.58 (d, 1H), 7.55 (s, 1H), 7.50 (dd, 1H), 7.29-7.7.21 (m, 5H), 7.19-7.10 (m, 3H), 7.03 (d, 2H), 6.52 (d, 1H), 3.40 (m, 1H), 1.88-1.73 (m, 4H), 1.68-1.55 (m, 1H), 1.40-1.32 (m, 1H); LCMS: 437 (M+H)⁺.

Example 211

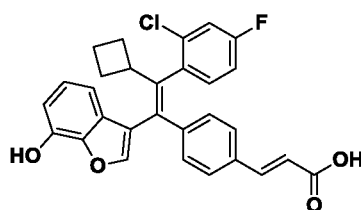
(E)-3-(4-((E)-2-(4-Carbamoyl-2-fluorophenyl)-1-(1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid



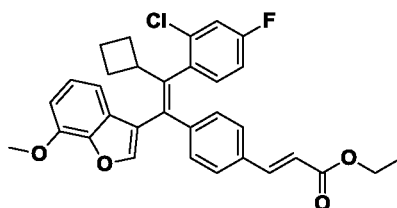
[00643] The title compound was isolated during the purification of Example 151. LCMS: 456 (M+H)⁺.

Example 212

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylic acid

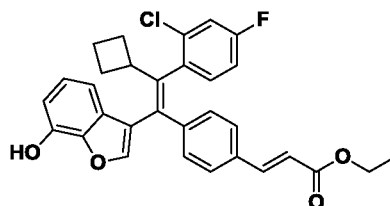


Step 1: (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylate



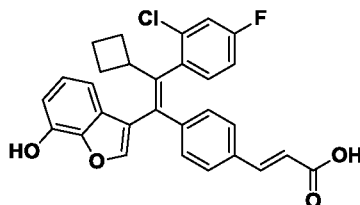
[00644] The title compound was prepared from Intermediate 30, 2-chloro-4-fluoriodobenzene, and 4-iodobenzaldehyde following General Procedures D and E. ¹H NMR (400MHz, DMSO-d₆): δ 8.06 (s, 1H), 7.48-7.39 (m, 4H), 7.35-7.31 (m, 1H), 7.18 (dt, 1H), 7.11 (t, 1H), 7.06 (d, 2H), 6.93 (d, 1H), 6.83 (d, 1H), 6.48 (d, 1H), 4.15 (m, 2H), 3.94 (s, 3H), 3.59-3.48 (m, 1H), 1.93-1.83 (m, 3H), 1.68-1.58 (m, 2H), 1.46-1.37 (m, 1H), 1.21 (t, 3H).

Step 2 : (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylate



[00645] A 20 mL vial equipped with a magnetic stir bar and N₂ inlet was charged with (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-methoxybenzofuran-3-yl)vinyl)phenyl)acrylate (110 mg, 0.21 mmol) and DCM (2 mL). The mixture was cooled to -78°C, and boron tribromide (621 μL, 1.0M solution in DCM, 0.62 mmol) was added dropwise. The reaction was stirred at -78°C, allowed to warm to room temperature over 2 h, cooled back to -78°C, and then quenched with MeOH. The mixture was diluted with DCM, washed with water, and then washed with brine. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified on a silica gel column eluted with 0-100% ethyl acetate in hexanes affording the title compound as yellow foam (91 mg). ¹H NMR (400MHz, DMSO-d₆): δ 10.05 (s, 1H), 8.01 (s, 1H), 7.50-7.39 (m, 4H), 7.34-7.31 (m, 1H), 7.18 (dt, 1H), 7.06 (d, 2H), 6.96 (t, 1H), 6.73 (d, 1H), 6.69 (d, 1H), 6.49 (d, 1H), 4.14 (q, 2H), 3.59-3.48 (m, 1H), 1.93-1.83 (m, 3H), 1.68-1.58 (m, 2H), 1.46-1.37 (m, 1H), 1.17 (t, 3H). LCMS: 515 (M-H)⁻.

Step 3: (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylic acid



[00646] The title compound was prepared from (E)-ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylate following General Procedure G. ¹H NMR (400MHz, DMSO-d₆): δ 12.25 (br s, 1H), 10.05 (s, 1H), 8.01 (d, 1H), 7.42-7.37 (m, 4H), 7.34-7.30 (m, 1H), 7.18 (dt, 1H), 7.06 (d, 2H), 6.96 (t, 1H), 6.73 (d, 1H), 6.68 (d, 1H), 6.37 (d, 1H), 3.55 (m, 1H), 1.95-1.83 (m, 3H), 1.71-1.58 (m, 2H), 1.46-1.37 (m, 1H). LCMS: 487 (M-H)⁻.

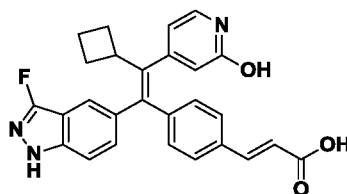
[00647] The Example in Table 18 was prepared following the procedures outlined for Example 212.

Table 18.

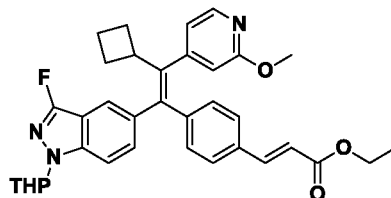
Example	Name	Structure	LCMS [M+H] ⁺
213	(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclobutyl-1-(7-hydroxybenzofuran-3-yl)vinyl)phenyl)acrylic acid		472

Example 214

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-hydroxypyridin-4-yl)vinyl)phenyl)acrylic acid

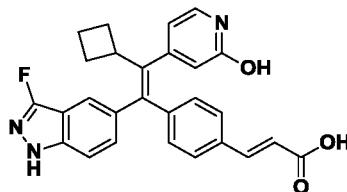


Step 1: (E)-Ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(2-methoxypyridin-4-yl)vinyl)phenyl)acrylate

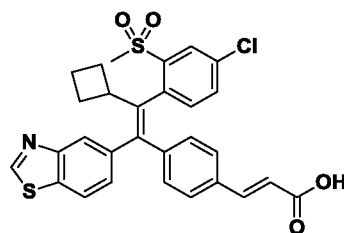


[00648] The title compound was prepared from Intermediate 14 following General Procedures D & E. LCMS: 582 (M+H)⁺.

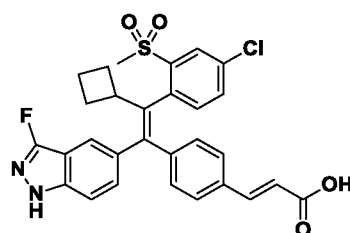
Step 2: (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-hydroxypyridin-4-yl)vinyl)phenyl)acrylic acid



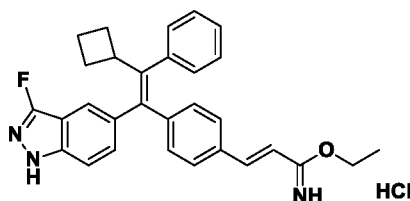
[00649] The title compound was prepared following General Procedures F (2M HCl in Et₂O and ethanol, reflux) and G. ¹H NMR (400 MHz, DMSO-d₆): δ 12.60 (s, 1H), 7.53 (s, 1H), 7.48-7.39 (m, 4H), 7.26-7.21 (m, 2H), 7.09 (d, 2H), 6.40 (d, 1H), 6.05 (m, 2H), 3.30 (m, 1H), 1.90-1.74 (m, 4H), 1.64-1.55 (m, 1H), 1.49-1.40 (m, 1H); LCMS: 456 (M+H)⁺.

Example 281**(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-(methylsulfonyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid**

[00650] The title compound was prepared from Intermediate 15, Intermediate 66 and Intermediate 45 following General Procedure D, Example 193 (Step 2), and General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.25 (s, 1H), 9.43 (s, 1H), 8.18 (d, 1H), 8.02 (s, 1H), 7.97 (s, 1H), 7.77 (d, 1H), 7.66 (d, 1H), 7.40 (m, 4H), 7.07 (d, 2H), 6.35 (d, 1H), 3.5 (m, 1H), 3.00 (s, 3H), 1.77-1.33 (m, 6H); LCMS: 550 (M+H)⁺.

Example 282**(E)-3-(4-((E)-2-(4-Chloro-2-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid**

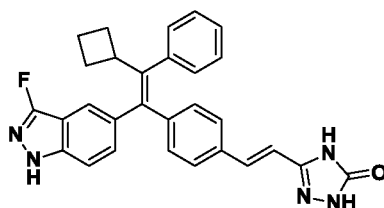
[00651] The title compound was prepared from Intermediate 14, Intermediate 66 and 4-iodobenzaldehyde following General Procedures D & E (*t*-butyl ester), Example 193 (Step 2), and General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.58 (s, 1H), 12.50-11.70 (br, 1H), 7.95 (d, 1H), 7.76 (dd, 1H), 7.63 (d, 1H), 7.60 (s, 1H), 7.50 (dd, 1H), 7.42-7.34 (m, 3H), 7.32 (dd, 1H), 7.04 (d, 2H), 6.36 (d, 1H), 3.53-3.43 (m, 1H), 2.97 (s, 3H), 1.78-1.60 (m, 2H), 1.59-1.48 (m, 3H), 1.40-1.30 (m, 1H); LCMS: 551 (M+H)⁺.

Intermediate 67**(E)-Ethyl 3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylimidate hydrochloride**

[00652] Hydrogen chloride gas was bubbled through a solution of Intermediate 57 (520 mg, 1.03 mmol) in toluene (7 mL) and ethanol (3 mL) for 1 h at 0 °C. The solution was kept at 0 °C overnight and concentrated under reduced pressure. The crude material was used as is for the next step. LCMS: 466(M+H)⁺.

Example 283

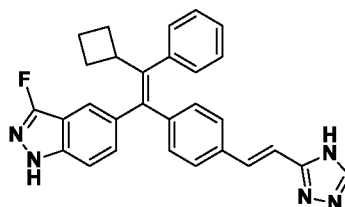
3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1H-1,2,4-triazol-5(4H)-one



[00653] A solution of Intermediate 67 (112 mg, 0.224 mmol), triethylamine (0.1 mL, 0.7 mmol), and ethyl hydrazinecarboxylate (50 mg, 0.48 mmol) in THF (2.5 mL) was heated at 80 °C overnight. The reaction was concentrated under reduced pressure and diluted with dioxane (2 mL) and water (2 mL). Potassium carbonate (920 mg, 6.66 mmol) was added to the reaction and the mixture was heated at 100 °C for 3 days. The mixture was diluted with ethyl acetate (20 mL), washed (2x20 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to yield the desired compound. ¹H NMR (400 MHz, DMSO-d₆): δ 12.57 (s, 1H), 11.62 (s, 1H), 11.50 (s, 1H), 7.55 (s, 1H), 7.48 (dd, 1H), 7.29-7.20 (m, 3H), 7.18-7.10 (m, 5H), 6.96 (d, 1H), 6.92 (d, 2H), 6.60 (d, 1H), 3.40 (m, 1H), 1.88-1.73 (m, 4H), 1.65-1.53 (m, 1H), 1.39-1.31 (m, 1H); LCMS: 478 (M+H)⁺.

Example 284

5-((E)-1-(4-((E)-2-(4H-1,2,4-Triazol-3-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole

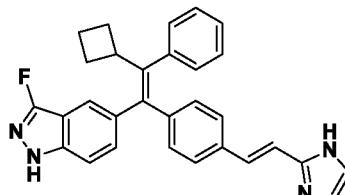


[00654] A solution of Intermediate 67 (135 mg, 0.269 mmol), triethylamine (0.1 mL, 0.7 mmol), and formohydrazide (35 mg, 0.58 mmol) in THF (3 mL) was heated at 80 °C overnight. The mixture was diluted with ethyl acetate (20 mL), washed (2x20 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to yield the desired compound. ¹H NMR (400 MHz, DMSO-d₆): δ 12.57 (s, 1H), 8.34 (s, 1H), 7.54 (s,

1H), 7.48 (dd, 1H), 7.33-7.22 (m, 6H), 7.20-7.11 (m, 4H), 7.01-6.92 (m, 3H), 3.40 (m, 1H), 1.88-1.73 (m, 4H), 1.65-1.53 (m, 1H), 1.39-1.31 (m, 1H); LCMS: 462 (M+H)⁺.

Example 285

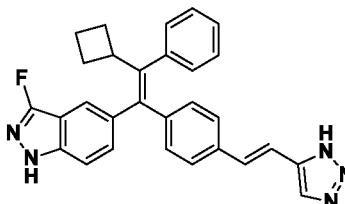
5-((E)-1-(4-((E)-2-(1H-Imidazol-2-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole



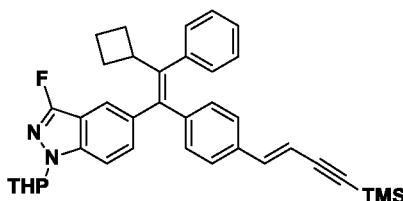
[00655] A solution of Intermediate 67 (130 mg, 0.259 mmol), triethylamine (0.1 mL, 0.7 mmol), and 2,2-diethoxyethanamine (42 μ L, 0.29 mmol) in THF (3 mL) was stirred at room temperature overnight. The reaction was concentrated under reduced pressure, diluted with formic acid (5 mL), and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (20 mL), washed (2x20 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to yield the desired compound. ¹H NMR (400 MHz, DMSO-d₆): δ 14.30 (s, 1H), 12.60 (s, 1H), 7.66 (s, 2H), 7.56-7.46 (m, 3H), 7.29-7.22 (m, 5H), 7.19-7.11 (m, 3H), 7.02 (d, 2H), 6.94 (d, 1H), 3.40 (m, 1H), 1.88-1.73 (m, 4H), 1.65-1.53 (m, 1H), 1.39-1.31 (m, 1H); LCMS: 461 (M+H)⁺.

Example 286

5-((E)-1-(4-((E)-2-(1H-1,2,3-Triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole

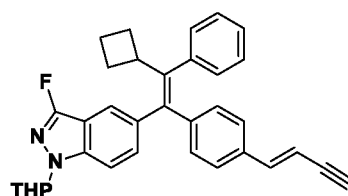


Step 1: 5-((E)-2-Cyclobutyl-2-phenyl-1-(4-((E)-4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



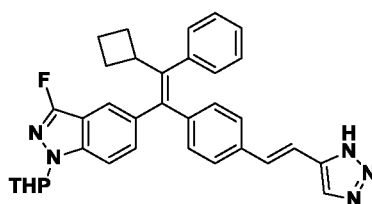
[00656] Butyllithium (1.6M in hexanes, 0.5 mL, 0.8 mmol) was added dropwise to a solution of triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (380 mg, 0.838 mmol) in THF (5 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min, and a solution of Intermediate 56 (201 mg, 0.418 mol) in THF (3 mL) was added. The reaction mixture was stirred at -78 °C for 1 h and stirred at 0 °C for an additional hour. The reaction was quenched with saturated ammonium chloride (5 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and purified on a silica gel column to yield the desired compound (120 mg) as a 2:1 mixture of trans/cis isomers. LCMS: 575 (M+H)⁺.

Step 2: 5-((E)-1-(4-((E)-But-1-en-3-yn-1-yl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



[00657] A solution of 5-((E)-2-cyclobutyl-2-phenyl-1-(4-((E)-4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenyl)vinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (115 mg, 0.20 mmol) and K₂CO₃ (5 mg, 0.04 mmol) in methanol (5 mL) was stirred at room temperature for 3h. The reaction was concentrated under reduced pressure and purified on a silica gel column to yield the desired compound (90 mg) as a 2.5:1 mixture of trans/cis isomers. LCMS: 503 (M+H)⁺.

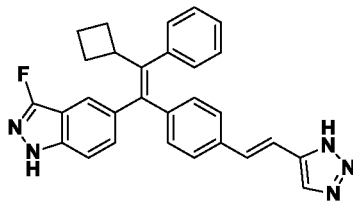
Step 3: 5-((E)-1-(4-((E)-2-(1H-1,2,3-Triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



[00658] To a solution of formaldehyde (37% in water, 0.2 mL, 2.7 mmol) and acetic acid (50 uL, 0.87 mmol) in dioxane (1 mL) was added sodium azide (18 mg, 0.28 mmol) and then 5-((E)-1-(4-((E)-but-1-en-3-yn-1-yl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (85 mg, 0.17 mmol) in dioxane (1 mL). The mixture was stirred for 10 min. Sodium ascorbate (8 mg, 0.04 mmol) and copper sulfate (0.1 M in water, 80 uL, 0.08 mmol) were added to the reaction, and the mixture was stirred for 2 days. The reaction mixture was diluted with ethyl acetate (20 mL), washed (2x20 mL H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The crude material was purified on a silica gel column to yield the desired compound (50 mg). ¹H NMR (400 MHz, DMSO-d₆): δ 7.97 (s, 1H), 7.75 (m, 1H), 7.54 (s, 1H), 7.35 (dd, 1H),

7.30-7.10 (m, 8H), 7.08 (d, 2H), 6.92 (d, 2H), 5.76 (m, 1H), 5.54 (d, 1H), 3.88 (m, 1H), 3.73 (m, 1H), 3.37 (m, 1H), 1.89-1.65 (m, 6H), 1.65-1.50 (m, 4H), 1.39-1.31 (m, 1H); LCMS: 546 (M+H)⁺.

Step 4: 5-((E)-1-(4-((E)-2-(1H-1,2,3-Triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole



[00659] The title compound was prepared from 5-((E)-1-(4-((E)-2-(1H-1,2,3-triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole following General Procedure F. ¹H NMR (400 MHz, DMSO-d₆): δ 12.57 (s, 1H), 7.97 (s, 1H), 7.53 (s, 1H), 7.49 (dd, 1H), 7.30-7.23 (m, 3H), 7.22-7.17 (m, 2H), 7.17-7.11 (m, 4H), 7.02 (d, 2H), 6.91 (d, 2H), 3.38 (m, 1H), 1.89-1.73 (m, 4H), 1.65-1.53 (m, 1H), 1.39-1.31 (m, 1H); LCMS: 462 (M+H)⁺.

Example A: 3x ERE MCF-7 Reporter Assay

[00660] MCF7 cells were maintained in RPMI 1640 supplemented with 10% FCS. Transcriptional assays were performed by seeding 100 μL of cells at a density of 250,000 cells/mL into 96-well cell culture plates in RPMI 1640 supplemented with 10% charcoal stripped serum. Cells were allowed to attach overnight, then transiently transfected using Lipofectin (Life Technologies) according to the manufacturer's protocol. Triplicate transfections were performed using 300 ng 3X ERE-TK-Luc (reporter vector), 50 ng CMVpRL (normalization vector), and 130 ng pCMX (filler DNA). Transfected cells were incubated overnight then treated with ligand. For ER agonist assays, the compounds were serially diluted and 50 μL of compound plus RPMI 1640 supplemented with charcoal stripped serum was added to the cells. For ER antagonist assays, the compounds were serially diluted, and 50 μL of compound with RPMI plus 17β-estradiol supplemented with charcoal stripped serum were added to the cells. The final 17β-estradiol concentration used in the antagonist assays was 0.1 nM. Following 24 hour incubation the medium was removed and the cells were lysed in 40 μL of lysis buffer (25mM Tris Phosphate, 2mM CDTA, 10% Glycerol, 0.5% Triton X-100, 2 mM DTT). Firefly luciferase activity was measured immediately following the addition of 40 μL luciferase buffer (20mM tricine, 0.1 mM EDTA, 1.07 mM (MgCo₃)₄ Mg(OH)₂•5H₂O, 2.67 mM MgSO₄, 33.3 mM DTT, 270 μM Coenzyme A, 470 μM luciferin, 530 μM ATP). Renilla luciferase was measured following the addition of 40 μL coelenterazine buffer (1.1 M NaCl, 2.2 mM Na₂EDTA, 0.22 M K₂PO₄ (pH 5.1), 0.44 mg/mL BSA, 1.3 mM NaN₃, 1.43 μM coelenterazine, final pH adjusted to 5.0).

Example B: Breast Cancer Cell Viability Assays

[00661] MCF-7 cells were adjusted to a concentration of 20,000 cells per mL in RPMI containing 10% FBS and 20 mM HEPES. 16 microliters of the cell suspension (320 cells) was added to each well of a 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 μ L at a final concentration ranging from 0.3-0.000003 μ M. After 5 days' compound exposure, 16 μ L of CellTiter-Glo (Promega, Madison WI) was added to the cells, and the relative luminescence units (RLUs) of each well were determined. CellTiter-Glo added to 32 μ L of medium without cells was used to obtain a background value. The Percent viability of each sample was determined as follows: $(\text{RLU sample} - \text{RLU background} / \text{RLU untreated cells} - \text{RLU background}) \times 100 = \% \text{viability}$.

[00662] Viability effects in additional ER+ breast cancer cell lines, including BT474, CAMA1, MDA-MB-361, ZR-75-1, T47D, can be profiled in assays similar to Example B.

Example C: Breast Cancer Cell ER- α In Cell Western Assay (SP1)

[00663] MCF-7 cells were adjusted to a concentration of 200,000 cells per mL in RPMI containing 10% charcoal-stripped FBS and 20 mM HEPES. 16 microliters of the cell suspension (3200 cells) was added to each well of a poly-D-lysine 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 μ L at a final concentration ranging from 0.3-0.000003 μ M. At 4 or 24 hr post compound addition, the cells were fixed (10% formalin in PBS) for 20 minutes. Cells were permeablized in PBS 0.1% Triton and blocked with LICOR blocking buffer (50 μ L/well, 90'). The wells were then incubated overnight at 4 $^{\circ}$ C with SP1 rabbit monoclonal Ab (Thermo Scientific) diluted 1:1000 in LICOR blocking buffer/0.1% Tween-20. Wells which were treated with blocking buffer with Tween but no antibody were used as a background control. Wells were washed with 0.1% Tween-20/PBS and then incubated in goat anti-rabbit IRDyeTM 800CW (LICOR Inc.; 1:10000) and DRAQ5 DNA dye (1:2000 for 2 mM stock) diluted in LICOR blocking buffer containing 0.1% Tween-20 and 0.01% SDS for 60 minutes. Cells were washed (50 μ L/well, 5' each) in 0.1% Tween-20/PBS. Plates were scanned on a LICOR Odyssey infrared imaging system. Integrated intensities in the 800 nm channel and 700 nm channel were measured to determine levels of ER and DNA respectively. Percent ER levels were determined as follows:
 $(\text{Integrated intensity 800 nm sample} / \text{Integrated intensity 700 nm sample}) / (\text{Integrated intensity 800 nm untreated cells} / \text{Integrated intensity 700 nm untreated cells}) \times 100 = \% \text{ER levels}$.

[00664] Effects on steady state levels of ER- α in additional ER+ breast cancer cell lines, including BT474, CAMA1, MDA-MB-361, ZR-75-1, T47D, can be profiled in assays similar to Example C.

[00665] Illustrative biological data for representative compounds disclosed herein is presented in the following table:

Table 19.

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
1	A	++	A	++
2	A	++	A	++
3	A	++	A	++
4	A	++	A	++
5	A	++	A	++
6	A	++	A	++
7	A	++	A	++
8	A	++	A	++
9	A	++	A	++
10	A	++	A	++
11	A	++	A	++
12	A	++	A	++
13	A	++	A	++
14	A	++	A	++
15	A	++	A	++
16	A	++	A	++
17	A	++	A	++
18	A	++	A	++
19	A	++	A	++
20	A	++	A	++
21	A	++	A	++
22	B	++	B	++
23	A	++	A	++
24	A	++	A	++
25	A	++	A	++
26	A	++	A	++
27	A	++	A	++
28	A	++	A	++
29	A	++	A	++
30	A	++	A	++
31	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
32	B	++	B	++
33	A	++	A	++
34	A	++	A	++
35	A	++	A	++
36	A	++	A	++
37	A	++	A	++
38	A	++	A	++
39	A	++	A	++
40	A	++	A	++
41	A	++	A	++
42	A	++	A	++
43	A	++	A	++
44	A	++	A	++
45	A	++	A	++
46	A	++	A	++
47	A	++	A	++
48	A	++	A	++
49	A	++	A	++
50	A	++	A	++
51	A	++	A	++
52	A	++	A	++
53	A	++	A	++
54	A	++	A	++
55	A	++	A	++
56	B	++	A	++
57	A	++	A	++
58	B	++	B	++
59	A	++	A	++
60	A	++	A	++
61	A	++	A	++
62	A	++	A	++
63	A	++	A	++
64	A	++	A	++
65	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
66	A	++	A	++
67	A	++	A	++
68	A	++	A	++
69	A	++	A	++
70	A	++	A	++
71	A	++	A	++
72	A	++	A	++
73	A	++	A	++
74	A	++	A	++
75	A	++	A	++
76	A	++	A	++
77	A	++	A	++
78	A	++	A	++
79	A	++	A	++
80	A	++	A	++
81	A	++	A	++
82	A	++	A	++
83	A	++	A	++
84	A	++	A	++
85	A	++	A	++
86	A	++	A	++
87	A	++	A	++
88	A	++	A	++
89	A	++	A	++
90	A	++	A	++
91	A	++	A	++
92	A	++	A	++
93	A	++	A	++
94	A	++	A	++
95	A	++	A	++
96	A	++	A	++
97	A	++	A	++
98	A	++	A	++
99	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
100	A	++	A	++
101	A	++	A	++
102	A	++	A	++
103	A	++	A	++
104	A	++	A	++
105	A	++	A	++
106	A	++	A	++
107	A	++	A	++
108	A	++	A	++
109	A	++	A	++
110	A	++	A	++
111	A	++	A	++
112	A	++	A	++
113	A	++	A	++
114	A	++	A	++
115	A	++	A	++
116	A	++	A	++
117	A	++	A	++
118	A	++	A	++
119	A	++	A	++
120	A	++	A	++
121	A	++	A	++
122	A	++	A	++
123	A	++	A	++
124	A	++	A	++
125	A	++	A	++
126	A	++	A	++
127	A	++	A	++
128	B	+	A	++
129	A	++	A	++
130	A	++	A	++
131	A	++	A	++
132	A	++	A	++
133	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
134	A	++	A	++
135	B	++	A	++
136	A	++	A	++
137	A	++	A	++
138	A	++	A	++
139	A	++	A	++
140	A	++	A	++
141	A	++	A	++
142	A	++	A	++
143	A	++	A	++
144	A	++	A	++
145	A	++	A	++
146	A	++	A	++
147	A	++	A	++
148	A	++	A	++
149	A	++	A	++
150	A	++	A	++
151	A	++	A	++
152	A	++	A	++
153	A	++	A	++
154	A	++	A	++
155	A	++	A	++
156	A	++	A	++
157	A	++	A	++
158	A	++	A	++
159	A	++	A	++
160	A	++	A	++
161	A	++	A	++
162	B	++	B	++
163	A	++	A	++
164	A	++	A	++
165	B	++	A	++
166	A	++	A	++
167	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
168	A	++	A	++
169	A	++	A	++
170	A	++	A	++
171	A	++	A	++
172	A	++	A	++
173	A	++	A	++
174	A	++	A	++
175	A	++	A	++
176	A	++	A	++
177	A	++	A	++
178	A	++	A	++
179	A	++	A	++
180	A	++	A	++
181	A	++	A	++
182	A	++	A	++
183	A	++	A	++
184	A	++	A	++
185	A	++	A	++
186	A	++	A	++
187	A	++	A	++
188	A	++	A	++
189	A	++	A	++
190	A	++	A	++
191	A	++	A	++
192	A	++	A	++
193	A	++	A	++
194	A	++	A	++
195	A	++	A	++
196	A	++	A	++
197	A	++	A	++
198	A	++	A	++
199	A	++	A	++
200	B	++	A	++
201	B	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
202	A	++	A	++
203	A	++	A	++
204	A	++	A	++
205	B	+	A	++
206	A	+	A	++
207	B	+	A	++
208	A	++	A	++
209	A	+	A	++
210	A	++	A	++
211	B	+	B	++
212	A	++	A	++
213	A	++	A	++
214	B	+	B	++
215	A	++	A	++
216	A	++	A	++
217	A	++	A	++
218	A	++	A	++
219	A	++	A	++
220	A	++	A	++
221	A	++	A	++
222	A	++	A	++
223	A	++	A	++
215	A	++	A	++
224	A	++	A	++
225	A	++	A	++
226	A	++	A	++
227	A	++	A	++
228	A	++	A	++
229	A	++	A	++
230	A	++	A	++
231	A	++	A	++
232	A	++	A	++
233	A	++	A	++
234	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
235	A	++	A	++
236	A	++	A	++
237	A	++	A	++
238	A	++	A	++
239	A	++	A	++
240	A	++	A	++
241	A	++	A	++
242	A	++	A	++
243	A	++	A	++
244	A	++	A	++
245	A	++	A	++
246	A	++	A	++
247	A	++	A	++
248	A	++	A	++
249	A	++	A	++
250	A	++	A	++
251	A	++	A	++
252	B	++	A	++
253	A	++	A	++
254	A	++	A	++
255	A	+	A	++
256	A	++	A	++
257	A	++	A	++
258	A	++	A	++
259	A	++	A	++
260	A	++	A	++
261	A	++	A	++
262	A	++	A	++
263	A	++	A	++
264	A	++	A	++
265	A	++	A	++
266	A	++	A	++
267	A	++	A	++
268	A	++	A	++

Example	MCF7 Viability Assay		ER- α In Cell Western Assay (SP1)	
	IC ₅₀	Max Response	IC ₅₀	Max Response
269	A	++	A	++
270	A	++	A	++
271	A	++	A	++
272	A	++	A	++
273	A	++	A	++
274	A	++	A	++
275	A	++	A	++
276	A	++	A	++
277	A	++	A	++
278	A	++	A	++
279	A	++	A	++
280	A	++	A	++
281	A	++	A	++
282	A	++	A	++
283	A	++	A	++
284	A	++	A	++
285	A	++	A	++
286	A	++	A	++

A = single IC₅₀ ≤ 100 nM; B = single IC₅₀ > 100 nM;
 + = a single % value < 40%; ++ = a single % value ≥ 40%

Example D: Ishikawa Uterine Cell Alkaline Phosphatase Assay

[00666] Subconfluent Ishikawa cells in a T225 are incubated 24 hours in an estrogen free basal medium (EFBM) consisting of DMEM:Ham's F-12 50:50 phenol red free basal medium containing 5% Charcoal Dextran treated FBS and 20 mM HEPES. Cells are plated the following day in EFBM in clear 384 well plates at a concentration of 2.5×10^5 cells per mL, 16 μ L per well (4000 cells per well). A 12 point semilog dilution of each compound is carried out in DMSO and subsequently diluted in EFBM. An equal volume of compound in EFBM is added immediately after plating cells, and the cells are incubated for 3 days. The cells are fixed with 5% formalin, and rinsed with PBS. Alkaline Phosphatase substrate 4-Nitrophenyl phosphate disodium salt hexahydrate is added (1 mg/mL final concentration) to a solution containing 2 mM MgCl₂, 1 M diethanolamine, and adjusted to pH 9.0. The substrate solution is added to the cell cultures (16 μ L per well), and OD₄₀₅ is measured in a multiwell plate spectrophotometer when the optical density at 405 nm wavelength of cells treated with 17 β -estradiol in the concentration range of 1-30 nM reaches 1.0-1.2 absorbance units. Cells treated with DMSO alone serve as a background control. Percent activity in

background subtracted samples is measured as follows: % activity = $\text{OD}_{405} \text{ sample} / \text{OD}_{405} \text{ max of } 17\beta\text{-estradiol treated cells} \times 100$.

Example E: Ovarian Cancer Cell Viability Assays

[00667] BG-1 cells are diluted in RPMI containing 10% FBS and 20 mM HEPES. 16 microliters of the cell suspension is added to each well of a 384 well plate, and the cells are incubated overnight. The following day an eleven point, serial semilog dilution of each compound is added to the cells in 16 μL at a final concentration ranging from 0.3-0.000003 μM . After 5 to 7 days' compound exposure, 16 μL of CellTiter-GLo (Promega, Madison WI) is added to the cells, and the relative luminescence units (RLUs) of each well is determined. CellTiter-Glo added to 32 μL of medium without cells is used to obtain a background value. The Percent viability of each sample is determined as follows: $(\text{RLU sample} - \text{RLU background} / \text{RLU untreated cells} - \text{RLU background}) \times 100 = \% \text{viability}$.

[00668] Viability effects in additional ER+ ovarian cancer cell lines, including OVKATE, OVSAHO, A1847, SKOV3, SW626, A2780, can be profiled in assays similar to Example E.

Example F: Ovarian Cancer Cell ER- α In Cell Western Assay

[00669] BG-1 cells are diluted in RPMI containing 10% charcoal-stripped FBS and 20 mM HEPES. 16 microliters of the cell suspension is added to each well of a poly-D-lysine 384 well plate, and the cells are incubated overnight. The following day an eleven point, serial semilog dilution of each compound is added to the cells in 16 μL at a final concentration ranging from 0.3-0.000003 μM . At 4 or 24 hr post compound addition, the cells are fixed (10% formalin in PBS) for 20 minutes. Following fixation the cells are permeabilized in PBS 0.1% Triton and blocked with LICOR blocking buffer (50 μL /well, 90'). The wells are then incubated overnight at 4 °C with SP1 rabbit monoclonal Ab (Thermo Scientific) diluted 1:1000 in LICOR blocking buffer/0.1% Tween-20. Wells treated with blocking buffer with Tween but no antibody are used as a background control. All wells are washed with 0.1% Tween-20/PBS and then incubated in goat anti-mouse IRDyeTM 800CW (LICOR Inc.; 1:10000) and DRAQ5 DNA dye (1:2000 for 2mM stock) diluted in LICOR blocking buffer containing 0.1% Tween-20 and 0.01% SDS for 60 minutes. Cells are then washed (50 μL /well, 5' each) in 0.1% Tween-20/PBS. Plates are scanned on a LICOR Odyssey infrared imaging system. Integrated intensities in the 800 nm channel and 700 nm channel are measured to determine levels of ER and DNA respectively. Percent ER levels are determined as follows:

$(\text{Integrated intensity } 800 \text{ nm sample} / \text{integrated intensity } 700 \text{ nm sample}) / (\text{Integrated intensity } 800 \text{ nm untreated cells} / \text{integrated intensity } 700 \text{ nm untreated cells}) \times 100 = \% \text{ER levels}$.

[00670] Effects on steady state levels of ER- α in additional ER+ ovarian cancer cell lines, including OVKATE, OVSAHO, A1847, SKOV3, SW626, A2780, can be profiled in assays similar to Example F.

[00671] Other cancer cell lines contemplated for testing compounds described herein include: ER-positive endometrial cell lines (Ishikawa, ECC1, HEC-1, EnCa-101) and ER-positive cervical cell lines (Caski, HeLa, SiHa).

Example G: Breast Cancer Model; Xenograft Assay (MCF-7)

[00672] Time release pellets containing 0.72 mg 17- β Estradiol were subcutaneously implanted into nu/nu mice. MCF-7 cells were grown in RPMI containing 10% FBS at 5% CO₂, 37 °C. Cells were spun down and re-suspended in 50% RPMI (serum free) and 50% Matrigel at 1X10⁷ cells/mL. MCF-7 cells were subcutaneously injected (100 μ L/animal) on the right flank 2-3 days post pellet implantation. Tumor volume (length x width²/2) was monitored bi-weekly. When tumors reached an average volume of ~200 mm³ animals were randomized and treatment was started. Animals were treated with Vehicle or Compound daily for 4 weeks. Tumor volume and body weight were monitored bi-weekly throughout the study. At the conclusion of the treatment period, plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example H: Breast Cancer Model; Xenograft Assay (MCF-7 derivative)

[00673] Female nu/nu mice (with supplemental 17- β Estradiol pellets; 0.72mg; 60 day slow release) bearing MCF-7 tumors (mean tumor volume 200mm³) were treated with Tamoxifen (citrate) by oral gavage. Tumor volume (length x width²/2) and body weight were monitored twice weekly. Following a significant anti-tumor response in which tumor volume remained static, evident tumor growth was first observed at approximately 100 days of treatment. At 120 days of treatment, tamoxifen dose was increased. Rapidly growing tumors were deemed tamoxifen resistant and selected for in vivo passage into new host animals. Tumor Fragments (~100mm³/animal) from the tamoxifen resistant tumors were subcutaneously implanted into the right flank of female nu/nu mice (with 17- β Estradiol pellets (0.72mg; 60 day slow release)). Passaged tumors were maintained under constant Tamoxifen selection, and Tumor volume (length x width²/2) was monitored weekly. When tumor volume reached ~150-250 mm³, animals were randomized into treatment groups (mean tumor volume 200 mm³) and tamoxifen treatment was terminated (except for a tamoxifen control arm). Animals were treated with Vehicle or Compound daily for 4 weeks. Tumor volume and body weight were monitored twice weekly for the duration of the study. At the conclusion of the treatment period; plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example I: Ovarian Cancer Model; Xenograft Assay (BG-1)

[00674] Time release pellets (0.72 mg 17- β Estradiol/60 days) are subcutaneously implanted into female nu/nu mice. BG-1 cells are grown in DMEM Ham's F-12 50/50 containing 10% FBS, 10 mM Sodium Pyruvate, 10 mM Non-Essential Amino Acids at 5% CO₂, 37 °C. Prior to injection, cells are trypsinized and suspended in 50% DMEM Ham's F-12 (serum free) and 50% Matrigel at 5X10⁷ cells/mL. BG-1 cells are subcutaneously injected (100 μ L/animal) on the right flank 2-3 days

post pellet implantation. Tumor volume (length x width²/2) is monitored bi-weekly. When tumors reach an average volume of ~250 mm³ animals are randomized and treatment started. Animals are treated with Vehicle or Compound daily. Tumor volume and body weight are monitored bi-weekly throughout the study. At the conclusion of the treatment period; plasma and tumor samples are taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example J: Immature Uterine Wet Weight-Antagonist Mode

[00675] Female immature CD-IGS rats (21 days old upon arrival) were treated for three days. Animals were dosed daily for three days. Vehicle or test compound was administered orally by gavage followed 15 minutes later by an oral dose of 0.1 mg/kg Ethynyl Estradiol. On the fourth day 24 hours after dose, plasma was collected for pharmacokinetic analysis. Immediately following plasma collection, the animals were euthanized and the uterus was removed and weighed.

Example K: Immature Uterine Wet Weight-Agonist Mode

[00676] Female immature CD-IGS rats (21 days old upon arrival) were treated for three days. Animals were dosed daily for three days. Vehicle or test compound was administered orally by gavage. On the fourth day 24 hours after dose, plasma was collected for pharmacokinetic analysis. Immediately following plasma collection, the animals were euthanized and the uterus was removed and weighed.

Example L: Breast Cancer Clinical Trial

[00677] A non-limiting example of a breast cancer clinical trial in humans is described below.

[00678] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as first- or second-line treatment of estrogen receptor (ER) positive metastatic breast cancer, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00679] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00680] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control.

[00681] Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00682] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each

dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00683] Eligibility: Female subjects that are 18 years and older.

[00684] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of invasive breast cancer, stage IV disease; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; post-menopausal status; ER positive breast cancer; HER2-negative breast cancer; up to one prior hormonal therapy for advanced or metastatic disease; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from treatment-related toxicity.

[00685] Exclusion Criteria: HER2-positive breast cancer; prior chemotherapy regimen for metastatic disease; history of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example M: Endometrial Carcinoma Clinical Trial

[00686] A non-limiting example of a endometrial carcinoma clinical trial in humans is described below.

[00687] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in the treatment of advanced or metastatic endometrial carcinoma, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00688] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00689] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control

Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00690] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00691] Eligibility: Female subjects that are 18 years and older.

[00692] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced or metastatic endometrial carcinoma; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; hormone receptor positive endometrial carcinoma; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00693] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example N: Ovarian Cancer Clinical Trial

[00694] A non-limiting example of an ovarian cancer clinical trial in humans is described below.

[00695] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, in the treatment of advanced ovarian cancer, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00696] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00697] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control

[00698] Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00699] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each dosing cycle, a physical exam, blood work (including tumor markers, e.g., CA-125) and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00700] Eligibility: Female subjects that are 18 years and older.

[00701] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced ovarian cancer; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; ER positive ovarian cancer; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00702] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example O: ER-Positive NSCLC Clinical Trial

[00703] A non-limiting example of an ER-positive non-small cell lung cancer (NSCLC) clinical trial in humans is described below.

[00704] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of advanced or metastatic estrogen receptor (ER) positive non-small cell lung cancer (NSCLC), collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00705] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00706] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control. Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c)

proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00707] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00708] Eligibility: Male and female subjects that are 18 years and older.

[00709] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced or metastatic ER-positive NSCLC; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00710] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example P: Endometriosis Clinical Trial

[00711] A non-limiting example of an endometriosis clinical trial in humans is described below.

[00712] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of patients with symptomatic/severe endometriosis, collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00713] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00714] Outcome Measures: The outcome measures of this study are symptoms improvement and/or pain relief and shrinkage of endometrial tissue.

[00715] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed.

[00716] Eligibility: Female subjects that are 18 years and older.

[00717] Inclusion Criteria: Diagnosis of symptomatic endometriosis; pre- or peri-menopausal status; ECOG performance status 0-1; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior surgery or treatment-related toxicity.

[00718] Exclusion Criteria: Pregnancy or lactating; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; concurrent investigational drug treatment; uncontrolled infection; active cardiac disease; serious medical or psychiatric illness.

Example Q: Uterine Leiomyoma Clinical Trial

[00719] A non-limiting example of an uterine leiomyoma in humans is described below.

[00720] Purpose: The purposes of this study are to assess the efficacy of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of patients with symptomatic uterine leiomyoma, collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00721] Intervention: Patients are administered 1-50 mg/kg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00722] Outcome Measures: The outcome measures of this study are symptoms improvement and/or pain relief and shrinkage of leiomyomas.

[00723] Detailed Description: Patients will be given a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed.

[00724] Eligibility: Female subjects that are 18 years and older.

[00725] Inclusion Criteria: Diagnosis of symptomatic uterine leiomyoma; pre- or peri-menopausal status; ECOG performance status 0-1; adequate liver and bone marrow function: AST <

2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior surgery or treatment-related toxicity.

[00726] Exclusion Criteria: Pregnancy or lactating; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; concurrent investigational drug treatment; uncontrolled infection; active cardiac disease; serious medical or psychiatric illness.

Example R: Parenteral Pharmaceutical Composition

[00727] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 100 mg of a water-soluble salt of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection

[00728] In another embodiment, the following ingredients are mixed to form an injectable formulation: 1.2 g of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, 2.0 mL of sodium acetate buffer solution (0.4 M), HCl (1 N) or NaOH (1 M) (q.s. to suitable pH), water (distilled, sterile) (q.s. to 20 mL). All of the above ingredients, except water, are combined and stirred and if necessary, with slight heating if necessary. A sufficient quantity of water is then added.

Example S: Oral Solution

[00729] To prepare a pharmaceutical composition for oral delivery, an aqueous 20% propylene glycol solution is prepared. To this is added a sufficient amount of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, to provide a 20 mg/mL solution.

Example T: Oral Capsule

[00730] To prepare a pharmaceutical composition for oral delivery, 100-500 mg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is mixed with starch. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[00731] In another embodiment, 100-500 mg of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

Example U: Oral Tablet

[00732] A tablet is prepared by mixing 48% by weight of a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, 45% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250 -500 mg.

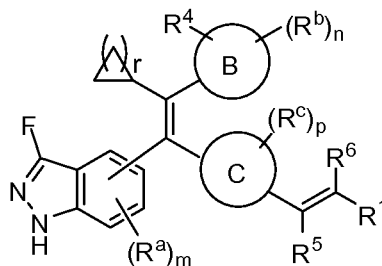
Example V: Topical Gel Composition

[00733] To prepare a pharmaceutical topical gel composition, a compound described herein (e.g. a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or a compound in Table 1), or a pharmaceutically acceptable salt thereof, is mixed with hydroxypropyl cellulose, propylene glycol, isopropyl myristate and purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

[00734] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (III), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (III)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or a 6-membered monocyclic heteroaryl;

R^1 is $-C(=O)-Z$, or a carboxylic acid bioisostere;

Z is $-OH$, $-OR^9$, $-NR^7R^8$, $-NR^7S(=O)_2R^9$, $-NHOH$ or $-NR^7OR^9$;

each R^a is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, and substituted or unsubstituted C_1-C_6 heteroalkyl;

each R^b is independently selected from H, halogen, $-NR^7R^8$, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-OCO_2R^9$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, $-NR^7C(=O)N(R^8)_2$, $-NR^7C(=O)R^9$, $-NR^7C(=O)OR^9$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_1-C_6 fluoroalkoxy, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-CN$, $-OH$, $-OR^9$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

R^4 is H, halogen, $-CN$, $-OH$, $-OR^9$, $-SR^8$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-NHS(=O)_2R^9$, $-S(=O)_2N(R^8)_2$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-OC(=O)N(R^8)_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, or C_1-C_6 heteroalkyl;

R^5 is H, C_1-C_4 alkyl, or halogen;

R^6 is H, C_1-C_4 alkyl, or halogen;

R^7 is H, or C_1-C_6 alkyl;

each R⁸ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R⁹ is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

provided that the compound is not

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-chloropyridin-4-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

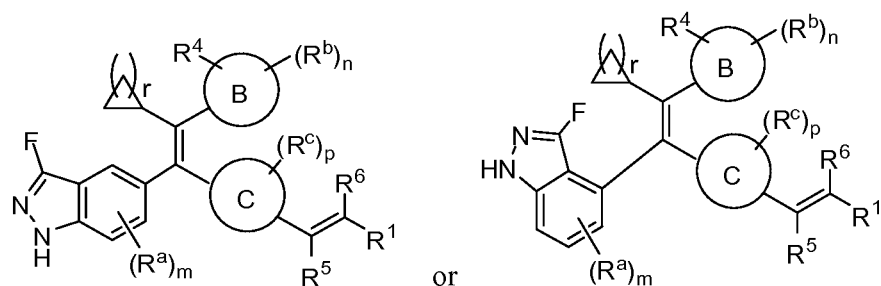
(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-cyclopropylacrylamide;

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

or

(E)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide.

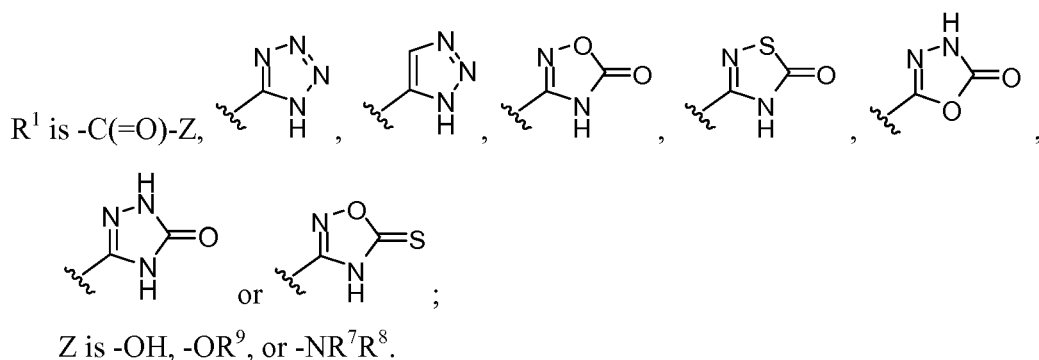
2. The compound of claim 1, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has any one of the following structures:



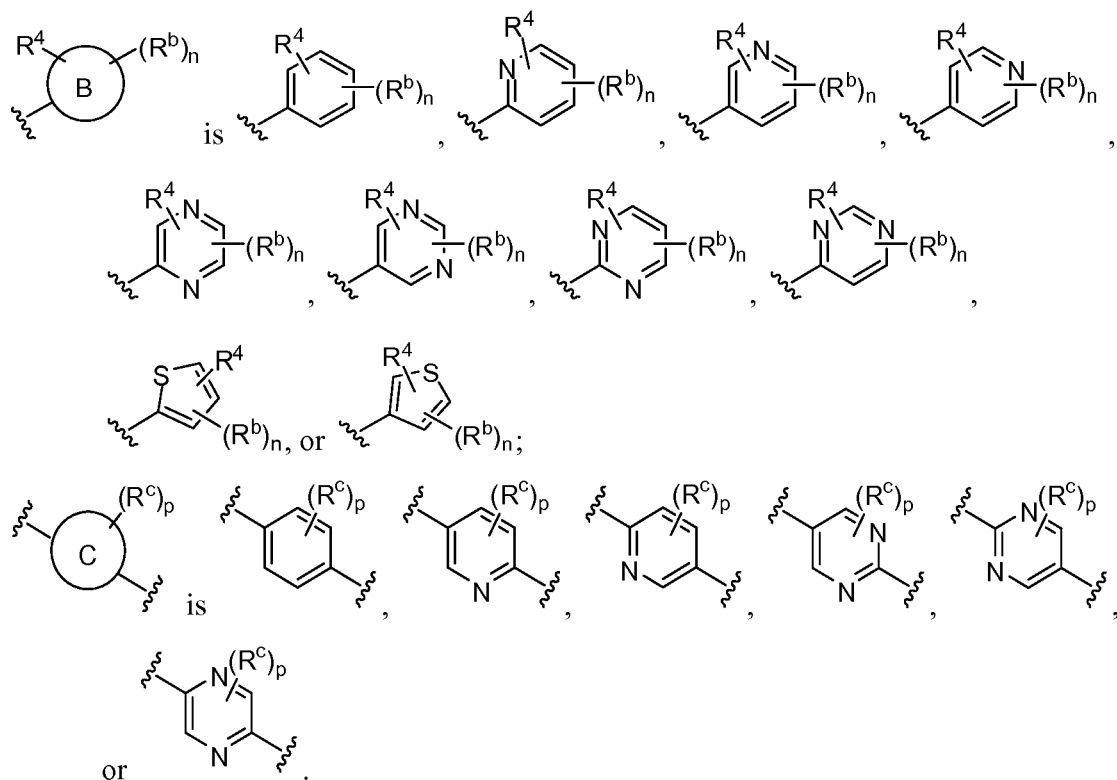
wherein:

ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl;

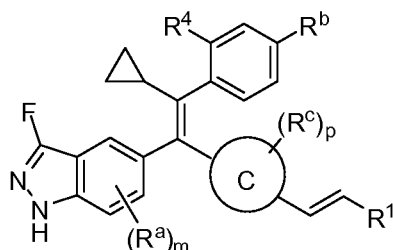
ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl;



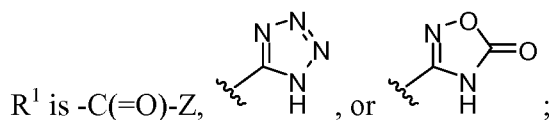
3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:



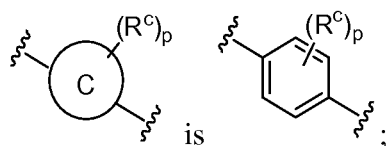
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:
r is 2.
5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has the following structure:



wherein,



Z is $-OH$;



R^a is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

R^b is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

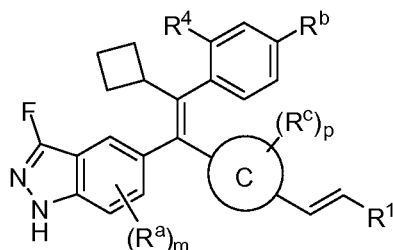
R^c is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, or $-CF_3$;

R^4 is H, F, Cl, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-S(=O)_2CH_3$, $-CH_3$, $-CF_3$, or $-CH_2OH$;

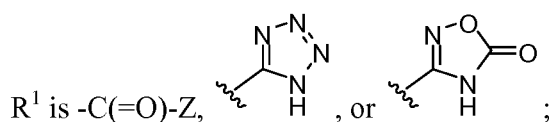
m is 0 or 1;

p is 0 or 1.

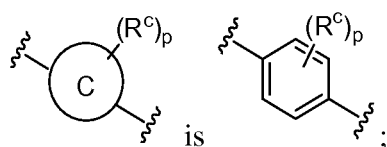
6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has the following structure:



wherein,



Z is -OH;



R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^b is Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

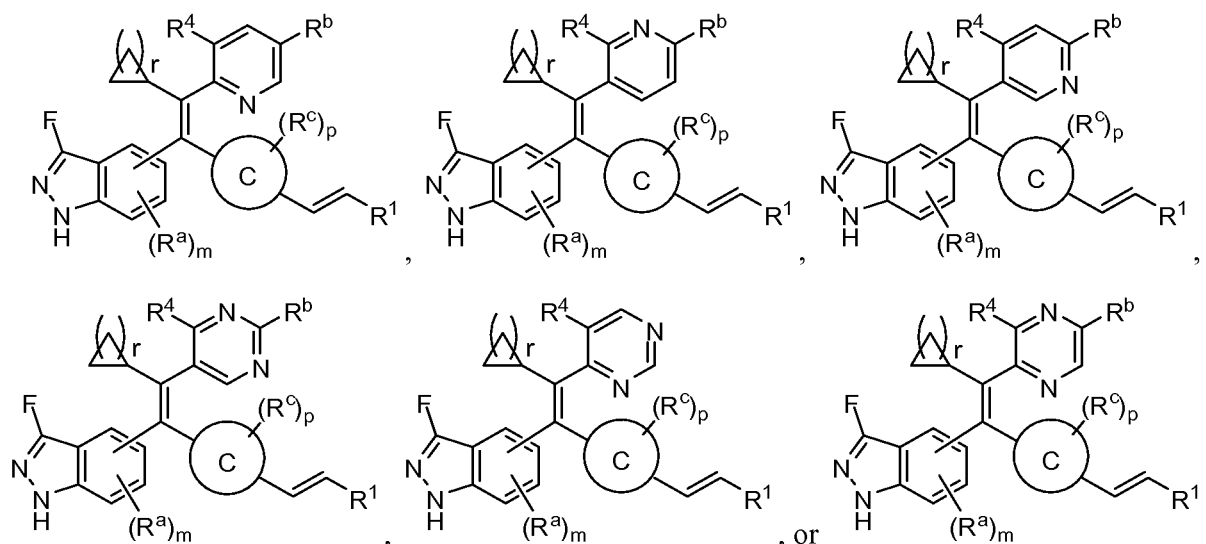
R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃;

R⁴ is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

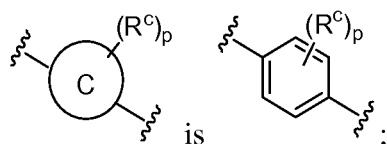
m is 0 or 1;

p is 0 or 1.

7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has any one of the following structures:



8. The compound of any one of claims 1-4, or 7, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein



R^a is H, F, Cl, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

R^c is H, F, Cl, -CN, -OH, -OR⁹, C₁-C₆alkyl, or C₁-C₆fluoroalkyl;

R⁴ is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

m is 0 or 1;

p is 0 or 1.

9. The compound of any one of claims 1-4, 7 or 8, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein

R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^b is Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃;

R^d is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH.

10. The compound of claim 1, wherein the compound is:

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyridin-2-yl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-2-methylphenyl)acrylic acid;

(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-methoxyphenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-((trifluoromethyl)sulfonyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(pyrrolidin-1-yl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxy-3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methoxy-4-(trifluoromethyl)pyrimidin-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-2-(6-ethoxy-4-methylpyridin-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-((5-(methylsulfonyl)pyrazin-2-yl)oxy)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(o-tolyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(pyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-fluoropyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-6-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methoxy-6-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-fluoro-6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-fluoro-6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methylpyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(pyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-fluoro-1H-indazol-5-yl)-2-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(6-methoxypyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(2,5-dimethylthiophen-3-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Cyano-2-fluorophenyl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Chloropyridin-4-yl)-2-cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(5-methoxy-3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyrazin-2-yl)acrylic acid;

(E)-3-(6-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyridin-3-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-fluoropyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)pyrimidin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-6-methoxypyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-3-methoxypyridin-2-yl)acrylic acid;

(E)-3-(3-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(2-Chloro-4-((Z)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

(E)-3-(5-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-(2-Chlorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)-3-fluoro-1H-indazole;

5-((E)-1-(4-((E)-2-(1H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)-N-(thiazol-2-yl)acrylamide;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(2,3-dihydroxypropyl)acrylamide;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-(1,3-dihydroxypropan-2-yl)acrylamide;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-N-methylacrylamide;

(E)-N-(2-Chloroethyl)-3-(4-((E)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylamide;

(E)-3-(4-((E)-2-Cyclopropyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid;

3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1-(2-hydroxyethyl)-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid;

3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylimidamide;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(2-hydroxypyridin-4-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-ethoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-4-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(5-Chloro-3-cyanopyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((Z)-2-(3-Chloro-5-fluoropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid;

(E)-3-(4-((Z)-2-Cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)-2-fluorophenyl)acrylic acid;

(E)-Ethyl 3-(4-((Z)-2-cyclobutyl-2-(3,5-dichloropyridin-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylate;

(E)-3-(4-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid;

(E)-3-(4-((E)-2-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4,6-bis(Trifluoromethyl)pyridin-3-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(5-((Z)-2-(3-Chloropyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(3-(trifluoromethyl)pyridin-2-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(4-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)-2-fluorophenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)but-2-enoic acid;

(E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)-2-methylacrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-2-(2,4-dichlorophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(5-((Z)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(4-((Z)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)-2-fluorophenyl)acrylic acid;

(E)-3-(5-((Z)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)pyridin-2-yl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-(trifluoromethyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

3-((E)-4-((E)-2-(2-Chloro-4-methoxyphenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

3-((E)-4-((E)-2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

2-((E)-1-Cyclobutyl-2-(3-fluoro-1H-indazol-5-yl)-2-(4-((E)-2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)vinyl)phenyl)vinyl)-5-(trifluoromethyl)benzonitrile;

(E)-3-(4-((E)-2-(4-Chloro-2-(methylsulfonyl)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

3-((E)-4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)styryl)-1H-1,2,4-triazol-5(4H)-one;

5-((E)-1-(4-((E)-2-(1H-1,2,3-Triazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-phenylvinyl)-3-fluoro-1H-indazole;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(o-tolyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2,4-difluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2,4-dichlorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropyl-2-(6-ethoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2,4-difluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-(trifluoromethyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2,4-dichlorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutyl-2-(6-ethoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(4-cyano-3-fluoro-1H-indazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyano-3-fluoro-1H-indazol-5-yl)-2-(2-cyano-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(4-ethoxyphenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(3-ethoxyphenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(4-ethoxy-2-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-Cyclobutyl-2-(3,5-dimethylthiophen-2-yl)-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(5-Cyano-3-methylthiophen-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethoxy)phenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

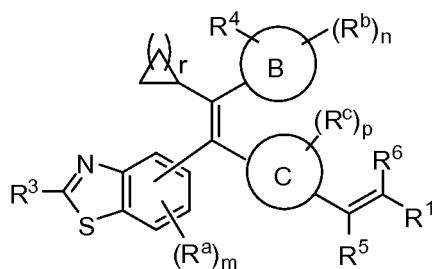
(E)-3-(4-((E)-2-(3-Chloro-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; or

(E)-3-(4-((E)-2-(3-Cyano-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid;

or a pharmaceutically acceptable salt, or N-oxide thereof.

11. A compound of Formula (XI), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (XI)

wherein,

ring B is phenyl, naphthyl, 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heteroaryl;

ring C is phenyl, 5-membered monocyclic heteroaryl or 6-membered monocyclic heteroaryl;

R¹ is -C(=O)-Z, or a carboxylic acid bioisostere;

Z is -OH, -OR⁹, -NR⁷R⁸, -NR⁷S(=O)₂R⁹, -NHOH or -NR⁷OR⁹;

R³ is H, halogen, -CN, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;

each R^a is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₆alkenyl, C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆fluoroalkyl, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^b is independently selected from H, halogen, -NR⁷R⁸, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -NHS(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -C(=O)N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁷C(=O)N(R⁸)₂, -NR⁷C(=O)R⁹, -

$\text{NR}^7\text{C}(=\text{O})\text{OR}^9$, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkynyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkoxy, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkoxy, substituted or unsubstituted phenyl and substituted or unsubstituted monocyclic heteroaryl;

each R^c is independently selected from H, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ fluoroalkyl;

R^4 is H, F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OR}^9$, $-\text{SR}^8$, $-\text{S}(=\text{O})\text{R}^9$, $-\text{S}(=\text{O})_2\text{R}^9$, $-\text{NHS}(=\text{O})_2\text{R}^9$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^9$, $-\text{OC}(=\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^8)_2$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ fluoroalkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl;

R^5 is H, $\text{C}_1\text{-C}_4$ alkyl, or halogen;

R^6 is H, $\text{C}_1\text{-C}_4$ alkyl, or halogen;

R^7 is H, or $\text{C}_1\text{-C}_6$ alkyl;

each R^8 is independently selected from H, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkynyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted benzyl;

each R^9 is independently selected from substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ fluoroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted benzyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

r is 1, 2, 3, or 4;

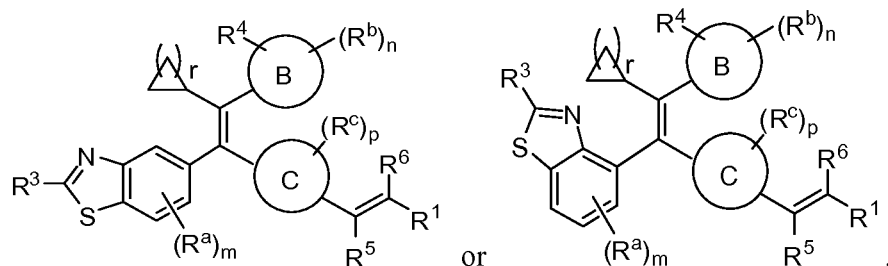
provided that the compound is not

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid; or
5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)benzo[d]thiazole.

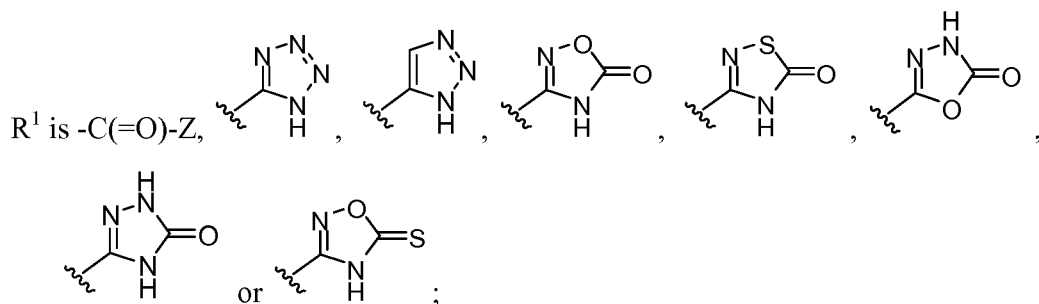
12. The compound of claim 11, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has any one of the following structures:



13. The compound of claim 11 or claim 12, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:
r is 1.
14. The compound of claim 11 or claim 12, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:
r is 2.
15. The compound of any one of claims 11-14, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:

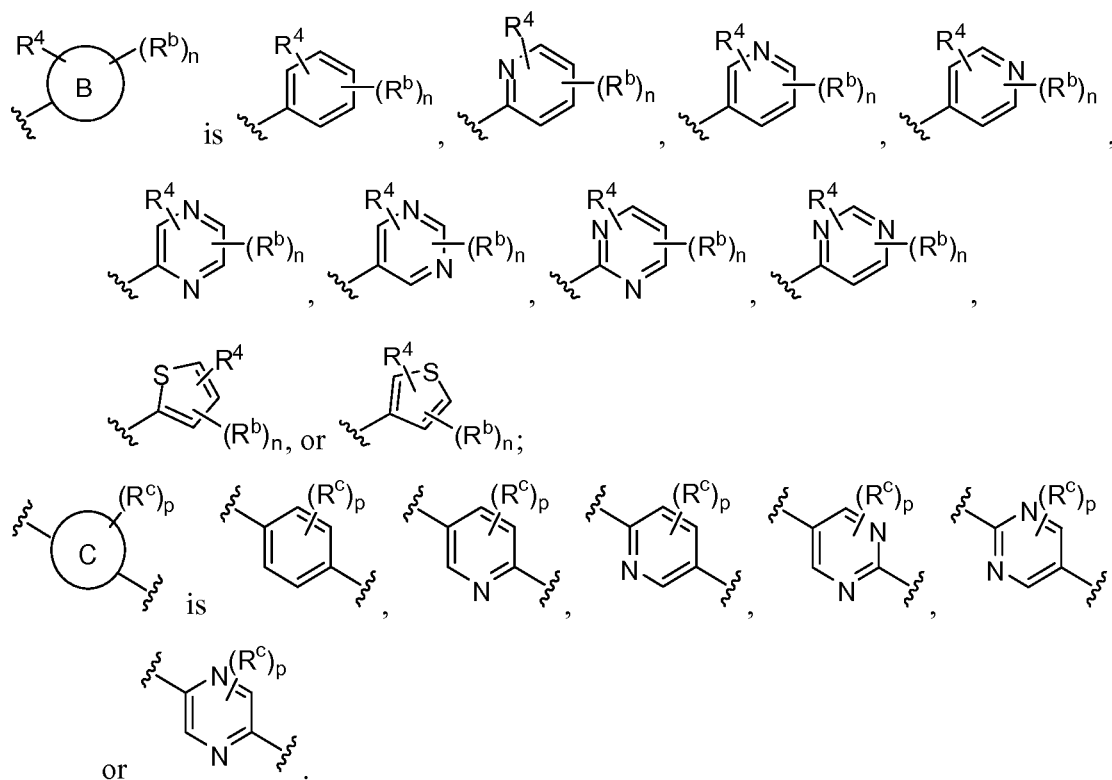
ring B is phenyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl;

ring C is phenyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl;

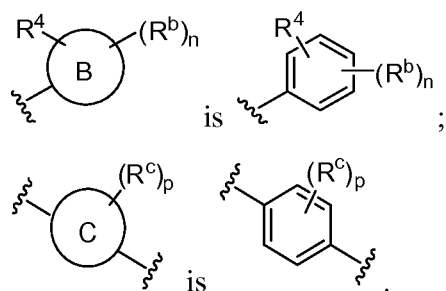


Z is -OH, -OR⁹, or -NR⁷R⁸.

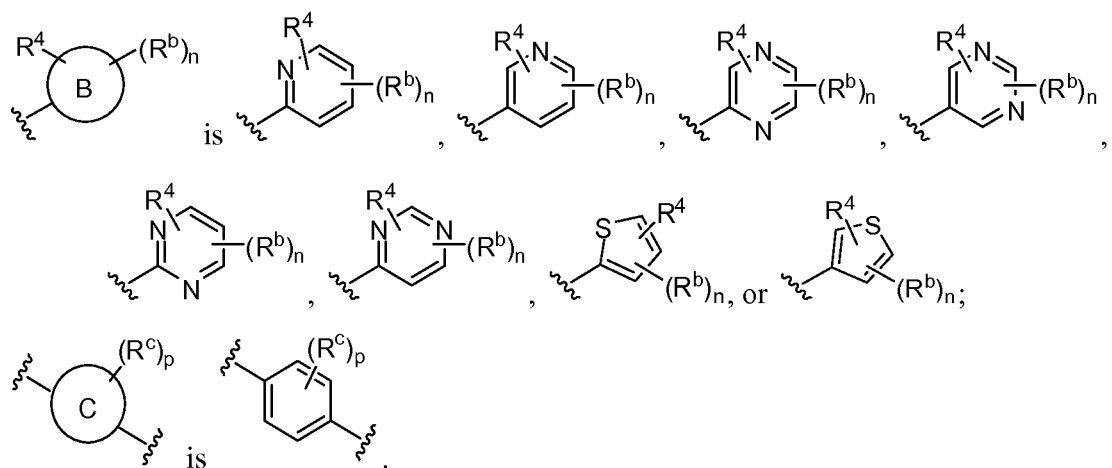
16. The compound of any one of claims 11-15, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:



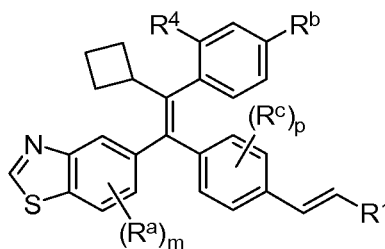
17. The compound of any one of claims 11-16, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:



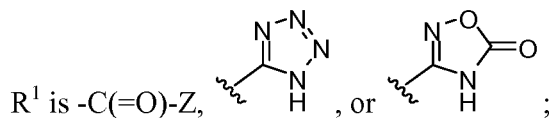
18. The compound of any one of claims 11-16, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein:



19. The compound of any one of claims 11-18, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein
 R^b is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl;
 R^4 is H, F, Cl, -CN, -OH, -OR⁹, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, C₁-C₆alkyl, C₁-C₆fluoroalkyl, or C₁-C₆heteroalkyl.
20. The compound of any one of claims 11-19, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein
 R^b is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;
 R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -OCF₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;
 R^5 is H;
 R^6 is H.
21. The compound of claim 11, or a pharmaceutically acceptable salt, or N-oxide thereof, wherein the compound has the following structure:



wherein,



Z is -OH;

R^a is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^b is Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

R^c is H, F, Cl, -CN, -OH, -OCH₃, -OCH₂CH₃, -CH₃, or -CF₃;

R^4 is H, F, Cl, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -S(=O)₂CH₃, -CH₃, -CF₃, or -CH₂OH;

m is 0 or 1;

p is 0 or 1.

22. The compound of claim 11, wherein the compound is:
 (E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-cyclobutyl-2-phenylvinyl)phenyl)acrylic acid;
 (E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyanothiophen-3-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(6-methoxypyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-fluorophenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-cyano-2-methylphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(2-chloro-4-fluorophenyl)-2-cyclobutylvinyl)benzo[d]thiazole;

5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-(3-chloropyridin-4-yl)-2-cyclobutylvinyl)benzo[d]thiazole;

5-((E)-1-(4-((E)-2-(2H-Tetrazol-5-yl)vinyl)phenyl)-2-cyclobutyl-2-(3-methylpyridin-4-yl)vinyl)benzo[d]thiazole;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methylthiophen-3-yl)vinyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-(methylsulfonyl)phenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-cyanophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(hydroxymethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chlorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-3-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-5-fluorophenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-(hydroxymethyl)-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(o-tolyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(4-methoxy-2-methylphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethoxy)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-(trifluoromethyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

3-((E)-4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-chloro-4-methoxyphenyl)-2-cyclobutylvinyl)styryl)-1,2,4-oxadiazol-5(4H)-one;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(4-chloro-2-(methylsulfonyl)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-fluoro-4-methoxyphenyl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(6-methoxy-4-methylpyridin-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(2,5-dimethylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2,5-dimethylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclobutyl-2-(3,5-dimethylthiophen-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(5-cyano-3-methylthiophen-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(3-methylpyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-cyclopropyl-2-(3-fluoropyridin-2-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloropyridin-2-yl)-2-cyclopropylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-cyanobenzo[d]thiazol-5-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(4-Cyanobenzo[d]thiazol-5-yl)-2-cyclobutyl-2-(2-methylthiophen-3-yl)vinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(2-cyano-4-(trifluoromethoxy)phenyl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-chloro-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-cyano-5-(trifluoromethyl)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid; or

(E)-3-(4-((E)-1-(Benzo[d]thiazol-5-yl)-2-(3-cyano-5-(trifluoromethoxy)pyridin-2-yl)-2-cyclobutylvinyl)phenyl)acrylic acid;

or a pharmaceutically acceptable salt, or N-oxide thereof.

23. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 22, or a pharmaceutically acceptable salt, or N-oxide thereof, and at least one pharmaceutically acceptable excipient.
24. The pharmaceutical composition of claim 23, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration.
25. The pharmaceutical composition of claim 23, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.
26. A compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of cancer in a mammal.
27. The compound of claim 26, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer in a mammal.
28. A compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of an estrogen receptor dependent or estrogen receptor mediated disease or condition in mammal.
29. The compound of claim 28, wherein the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from cancer, central nervous system (CNS) defects, cardiovascular system defects, hematological system defects, immune and inflammation diseases, susceptibility to infection, metabolic defects, neurological defects, psychiatric defects and reproductive defects.
30. A compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, cervical cancer, lung cancer, leiomyoma, uterine leiomyoma, hot flashes, alcoholism, migraine, aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension, deep vein thrombosis, Graves' Disease, arthritis, multiple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, migraine, vertigo, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis, age of menarche, endometriosis, or infertility in a mammal.