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TARGETING ALLOSTERIC AND ORTHOSTERIC POCKETS OF PHOSPHOINOSITIDE 3-KINASE (PI3K) FOR THE TREATMENT OF DISEASE

Cross-Reference to Related Patent Applications

[1] The present application claims the benefit of priority to U.S. Provisional Application No., 63/501,614, filed on May 11, 2023; U.S. Provisional Application No. 63/382,980, filed on November 9, 2022; and U.S. Provisional Application No. 63/382,029, filed on November 1, 2022; the contents of which are incorporated herein by reference in their entireties.

Reference to a Sequence Listing

[2] The present application is being filed along with a Sequence Listing in ST.26 XML format. The Sequence Listing is provided as a file titled "30449SequenceListing.xml" created October 30, 2023 and is 2,777 bytes in size. The Sequence Listing information in the ST.26 XML format is incorporated herein by reference in its entirety.

Field

[3] The present invention is directed to inhibitors of phosphoinositide 3-kinase (PI3K) and combinations thereof which are useful in the treatment of diseases, or disorders associated with PI3K modulation. The present invention also is directed to allosteric chromenone inhibitors of phosphoinositide 3-kinase (PI3K) useful in the treatment of diseases, or disorders associated with PI3K modulation, and the use of allosteric chromenone inhibitors in combination with other allosteric or orthosteric inhibitors of PI3K useful in the treatment of diseases, or disorders associated with PI3K modulation. The present invention also is directed toward inhibitors of PI3K and combination thereof, methods of (or uses for) treating a disease, or disorder associated with PI3K (e.g., CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS),

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breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer), and using, or methods of using, PI3K inhibitors in combination with one or more additional cancer therapies.

Background

[4] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling also is involved in other disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[5] PI3Ks are members of a unique, and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110 α , p110 β , p110 δ , and p110 γ) are typically activated by tyrosine kinases, or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the pathways of Akt/PDK1, mTOR, the Tec family kinases, and the Rho family GTPases. The class II, and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P, and PI(3,4)P₂.

[6] The PI3K isoforms have been implicated, for example, in a variety of human cancers, and disorders. The alpha (α) isoform of PI3K has been implicated, for example, in a variety of human cancers. Angiogenesis has been shown to selectively require the α isoform of PI3K in the control of endothelial cell migration. Mutations in the gene coding for PI3K α , or mutations which lead to upregulation of PI3K α are believed to occur in many human cancers such as lung, stomach, endometrial, ovarian, bladder, breast, colon, brain, prostate, and skin cancers. Mutations in the gene coding for PI3K α are point mutations clustered within several hotspots in helical, and kinase domains, such as E542K, E545K, and H1047R. Many of these mutations have been shown to be

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oncogenic gain-of-function mutations. Because of the high rate of PI3K α mutations, targeting of this pathway may provide valuable therapeutic opportunities. While other PI3K isoforms such as PI3K δ , or PI3K γ are expressed primarily in hematopoietic cells, PI3K α , along with PI3K β , is expressed constitutively.

[7] Due to the central role of PI3K α in regulating organismal glucose homeostasis, PI3K inhibition in patients often gives rise to adverse events which include hyperglycemia and/or hyperinsulinemia. High levels of circulating insulin could potentially be mitogenic and/or antiapoptotic for cancer cells, and thus negate the antiproliferative effects of PI3K inhibitors. In the setting of cancer with mutated PI3K α , one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic PI3K α inhibition would be to develop inhibitors with enhanced selectivity for mutant PI3K α over wild-type PI3K α . This would create an increased window for drug dosing to selectively inhibit the pathologic signaling of mutant PI3K α in the cancer cells without affecting the wild-type PI3K α in the host tissues that control systemic metabolism, thus limiting toxicities, and permitting higher doses, and more complete inhibition of the drug target.

[8] PI3K α has an ATP-binding pocket which may be targeted in order to modulate PI3K α activity. PI3K α must bind ATP in order to catalyze the transfer of a phosphate group from ATP to the 3'-OH group on phosphatidylinositols or phosphoinositides. Almost all PI3K inhibitors tested in clinical trials are antagonists that interact within the PI3K α ATP-binding pocket and compete with ATP as orthosteric inhibitors. The PI3K α ATP-binding pocket may alternatively be referred to as "the PI3K α orthosteric binding pocket."

[9] Current PI3K α inhibitors are nearly equipotent to wild-type and mutant PI3K α . Mutant selective inhibitors have been elusive due to the fact that the most common PI3K α mutations (E542K, E545K, and H1047R) are located far from the PI3K α orthosteric binding pocket. As such, inhibitors which target a second, peripheral binding pocket near a known mutation (e.g., H1047R) may provide a route to selective PI3K α inhibition.

[10] The present invention provides a new class of kinase inhibitors that target a non-ATP binding pocket of PI3K α which is referred to herein as "the PI3K α allosteric pocket 1" and may interact with amino acid residues of PI3K α including R1047. The disclosed kinase inhibitors target PI3K α .

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allosteric pocket 1 and may be utilized in combination therapies, for example, combination therapies in which the disclosed PI3K α inhibitors are used in combination with PI3K α inhibitors that target other pockets of PI3K α , such as the PI3K α orthosteric pocket.

[11] The present invention also provides a characterization of another non-ATP binding pocket of PI3K α , which is referred to as “the PI3K α allosteric pocket 2,” and the interaction of inhibitors of PI3K α with the PI3K α allosteric pocket 2. The disclosed kinase inhibitors which target PI3K α allosteric pocket 1 may be used in combination therapies with PI3K α inhibitors that target the PI3K α allosteric pocket 2.

Summary

[12] The disclosure relates to the use of inhibitors of phosphoinositide 3-kinase (PI3K) that target allosteric and orthosteric pockets of PI3K in methods of treating, preventing, or ameliorating a disease, or disorder, (or uses in the treatment, prevention, or amelioration of a disease, or disorder), in which PI3K plays a role. The PI3K inhibitors may be utilized in combination and may target an allosteric pocket of phosphatidylinositol 3-kinase alpha (PI3K α) referred to herein as “PI3K α allosteric pocket 1,” an allosteric pocket of PI3K α referred to herein as “PI3K α allosteric pocket 2,” or the PI3K α orthosteric pocket. (*See* Fig. 1). In some aspects of the disclosed methods, a PI3K α inhibitor may target the PI3K α allosteric pocket 1, the PI3K α allosteric pocket 2, or the PI3K α orthosteric pocket of a PI3K α mutant that is resistant to treatment with another PI3K α inhibitor, for example a PI3K α inhibitor that targets a different pocket of PI3K α .

[13] The methods may include administering to a patient in need thereof a therapeutically effective amount of a PI3K inhibitor of the present invention or combinations of PI3K inhibitors of the present invention and other PI3K inhibitors, which may include other allosteric inhibitors of PI3K and orthosteric inhibitors of PI3K. The methods and PI3K inhibitors of the present invention can be used in the treatment of a variety of PI3K-dependent or PI3K-associated diseases, and disorders.

[14] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α . The methods may comprise administering to a patient in need thereof: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first

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PI3K α selective inhibitor binds to the PI3K α allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to the PI3K α orthosteric pocket.

[15] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α . The methods may comprise administering to a patient in need thereof: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds to the PI3K α allosteric pocket 2; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to the PI3K α orthosteric pocket.

[16] In some aspects, the disclosed methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds to PI3K α allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to PI3K α allosteric pocket 2.

[17] In some aspects, the disclosed methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds to PI3K α allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor which is different from the first PI3K α selective inhibitor, wherein the second different PI3K α selective inhibitor binds to the PI3K α allosteric pocket 1. In some aspects, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor competitively bind to PI3K α allosteric pocket 1.

[18] In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor are administered simultaneously, separately, or sequentially. In some embodiments, the second PI3K α selective inhibitor is administered to the patient if the patient has a disease or disorder that is resistant to treatment with the first PI3K α selective inhibitor. In some embodiments, the second PI3K α selective inhibitor is administered to the patient after the disease or disorder of the patient has acquired resistance to treatment with the first PI3K α selective inhibitor.

[19] In some aspects of the disclosed methods which comprise administering a therapeutically

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effective amount of a first PI3K α selective inhibitor and a therapeutically effective amount of a second PI3K α selective inhibitor, an additive effect or synergistic effect may be observed. In some aspects of the disclosed methods, the therapeutically effective amount of the first PI3K α selective inhibitor administered in the disclosed methods may be less than a therapeutically effective amount of the first PI3K α selective inhibitor that is required in a treatment method where the second PI3K α selective inhibitor is not administered. In some aspects of the disclosed methods, the therapeutically effective amount of the second PI3K α selective inhibitor administered in the disclosed methods may be less than a therapeutically effective amount of the second PI3K α selective inhibitor that is required in a treatment method where the first PI3K α selective inhibitor is not administered.

[20] In some aspects of the disclosed methods, the therapeutically effective amount of the first PI3K α selective inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. In some aspects of the disclosed methods, the therapeutically effective amount of the second PI3K α selective inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. Adverse events may include, but are not limited to hyperglycemia, hyperinsulinemia, diarrhea, dehydration, skin rash, lymphopenia, increased alanine transaminase, fatigue, anemia, elevated serum lipase, anorexia, stomatitis, vomiting, weight loss, hypocalcemia, hypoglycemic disorder, alopecia, prolonged activated partial thromboplastin time, kidney disease with reduction in glomerular filtration rate (GFR), acute abdominal pain, and abnormal hepatic function tests.

[21] In some aspects, the disclosed methods relate to methods for treating a disease or disorder that is associated with modulation of PI3K α in a patient that has a disease or disorder that is resistant to treatment with a PI3K α selective inhibitor, which may be a PI3K α selective allosteric inhibitor or a PI3K α selective orthosteric inhibitor. The methods may comprise administering to the patient a different PI3K α selective inhibitor to which the disease or disorder is not resistant, such as a PI3K α selective allosteric inhibitor or a PI3K α selective orthosteric inhibitor.

[22] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient that has a disease or disorder that is resistant to

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treatment with a PI3K α selective orthosteric inhibitor. In some aspects, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3K α in a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3K α selective orthosteric inhibitor or in a patient that is identified as having a disease or disorder which exhibits an incomplete response to treatment with a PI3K α selective orthosteric inhibitor. In some aspects, the methods may comprise administering to a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3K α selective orthosteric inhibitor or that is identified as having a disease or disorder that exhibits an incomplete response to treatment with a PI3K α selective orthosteric inhibitor, a therapeutically effective amount of a PI3K α selective allosteric inhibitor, wherein the PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1. In some aspects, the methods may comprise administering to a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3K α selective orthosteric inhibitor or that is identified as having a disease or disorder which exhibits an incomplete response to treatment with a PI3K α selective orthosteric inhibitor, a therapeutically effective amount of a PI3K α selective allosteric inhibitor, wherein the PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 2.

[23] In some aspects, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a first PI3K α selective allosteric inhibitor, wherein the first PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1. In some aspects, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1. In some aspects, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2. In some aspects, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a PI3K α selective inhibitor that binds to the PI3K α orthosteric pocket.

[24] In some aspects, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a first PI3K α selective allosteric inhibitor,

wherein the first PI3K α selective allosteric inhibitor binds to PI3K α allosteric pocket 2. In some aspects, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1. In some aspects, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a PI3K α selective inhibitor that binds to the PI3K α orthosteric pocket.

[25] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient has been treated previously with a therapeutically effective amount of a PI3K α selective inhibitor, and the disease or disorder of the patient has acquired resistance to treatment with the PI3K α selective inhibitor. The method may include administered to the patient a different PI3K α selective inhibitor to which the disease or disorder is not resistant.

[26] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient previously has been treated with a therapeutically effective amount of a PI3K α selective allosteric inhibitor, wherein the PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1 or the PI3K α allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor, and the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective orthosteric inhibitor. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to

treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1.

[27] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient previously has been treated with a therapeutically effective amount of a PI3K α selective allosteric inhibitor, wherein the PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1 or the PI3K α allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor, and the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective orthosteric inhibitor. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1.

[28] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient has a disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation). The methods may comprise administering to the patient having the disease or disorder a therapeutically effective amount of a PI3K α selective orthosteric inhibitor. The methods may comprise

administering to the patient having the disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation) a therapeutically effective amount of a PI3K α allosteric inhibitor, wherein the PI3K α allosteric inhibitor binds to the PI3K α allosteric pocket 1. The methods may comprise administering to the patient having the disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation) a therapeutically effective amount of a PI3K α selective allosteric inhibitor that binds the PI3K α allosteric pocket 2.

[29] In some aspects, the methods related to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, such as a patient having a disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation). The methods may comprise determining that the patient has a disease or disorder comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), for example, by ordering or performing a genomic analysis. If the patient is found to have a disease or disorder comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), the methods further may comprise administering treatment to the patient, which may include administering one or more PI3K α selective inhibitors to the patient, which may include allosteric inhibitors (e.g., an allosteric inhibitor that binds to the PI3K α allosteric pocket 1 and/or an allosteric inhibitor that binds to the PI3K α allosteric pocket 2), orthosteric inhibitors, or combinations thereof as disclosed herein.

[30] In some aspects, the disclosed methods comprise selecting a patient for treatment with one or more PI3K α selective inhibitors. In some aspects, the patient is selected based on the patient having disease or disorder comprising a M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation). Optionally, a selected patient may be administered treatment, which may include administering one or more PI3K α selective inhibitors to the patient, which may include allosteric inhibitors (e.g.,

allosteric inhibitor that binds to the PI3K α allosteric pocket 1 or an allosteric inhibitor that binds to the PI3K α allosteric pocket 2), orthosteric inhibitors, or combinations thereof as disclosed herein.

[31] In the disclosed methods, a patient in need thereof may have cancer. In some aspects, the patient in need thereof may have breast cancer. In some aspects, the patient in need thereof may have PIK3CA-mutated, advanced, or metastatic breast cancer. In some aspects, the patient in need thereof may have PIK3CA H1047R-mutant advanced, or metastatic breast cancer that is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[32] In the disclosed methods, a patient in need thereof may have cancer and may have been previously administered one or more therapeutic agents for treating the cancer, which may include a PI3K α selective inhibitor. In some aspects, the patient may have a cancer which exhibits *de novo* resistance or acquired resistance to treatment with a therapeutic agent, which may include a PI3K α selective inhibitor, and the patient may be administered a different therapeutic agent, which may include a different PI3K α selective inhibitor.

[33] In the disclosed methods, the patient may have not been previously administered a therapeutic agent for treating the cancer, which may include a PI3K α selective inhibitor. In some aspects, the patient may be characterized as naïve to treatment with a PI3K α selective inhibitor.

Brief Description of the Figures

[34] Fig. 1. Schematic illustration of PI3K α (H1047R) showing Orthosteric pocket, Allosteric pocket 1, and Allosteric pocket 2.

[35] Fig. 2. Dose response curve for alpelisib in a T47D (M1043I+H1047R) (double, in *cis*, 6 $\times$) cell proliferation assay.

[36] Fig. 3. Dose response curve for Compound 21 in a T47D (M1043I+H1047R) (double, in *cis*, 6 $\times$) cell proliferation assay.

[37] Fig. 4. Dose response curve for Compound N1 in a T47D (M1043I+H1047R) (double, in *cis*, 6 $\times$) cell proliferation assay.

[38] Fig. 5. Dose response curve for Compound N2 in a T47D (M1043I+H1047R) (double, in *cis*, 6 $\times$) cell proliferation assay.

[39] Fig. 6. Dose response curve for Compound 1 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[40] Fig. 7. Dose response curve for Compound HP1 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[41] Fig. 8. Dose response curve for alpelisib in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[42] Fig. 9. Dose response curve for Compound HP1 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[43] Fig. 10. Dose response curve for Compound 1 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[44] Fig. 11. Dose response curve for Compound 21 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[45] Fig. 12. Combination Index plot for Compound 21 and alpelisib in T47D naïve cells based on growth inhibition assay (CTG).

[46] Fig. 13. Combination Index plot for Compound 21 and alpelisib in T47D (M1043I+H1047R) (double, in *cis*, 6×) cells based on growth inhibition assay (CTG).

[47] Fig. 14. Combination Index plot for Compound 21 and Compound HP1 in T47D naïve cells based on growth inhibition assay (CTG).

[48] Fig. 15. Combination Index plot for Compound 21 and Compound HP1 in T47D (M1043I+H1047R) (double, in *cis*, 6×) cells based on growth inhibition assay (CTG).

[49] Fig. 16. Combination Index plot for Compound 21 and alpelisib in MDA453 naïve cells based on growth inhibition assay (CTG).

[50] Fig. 17. Combination Index plot for Compound 21 and alpelisib in MDA453 (Cpd 21-R) (double, in *cis*, 6×) cells based on growth inhibition assay (CTG).

[51] Fig. 18. Combination Index plot for Compound 21 and Compound HP1 in MDA453 naïve cells based on growth inhibition assay (CTG).

[52] Fig. 19. Combination Index plot for Compound 21 and Compound HP1 in MDA453 (Cpd 21-R) cells based on growth inhibition assay (CTG).

[53] Fig. 20. Graphic illustration of the interaction of PIK α _H1047R and Compound 21 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the carboxy acid group of Compound 21 and the side chains of R1047 and Q981; hydrogen bonding between the carboxy acid group of Compound 21, a bridging water molecule, and the side chain of Y985; hydrogen bonding between the chromenone exocyclic ketone group of Compound 21, a bridging water molecule, and the side chain of H931 (and between the exocyclic ketone group of Compound 21, a bridging water molecule and the carbonyl backbone group of C901 (not shown)).

[54] Fig. 21. Graphic illustration of the interaction of PIK α _H1047R and Compound 172 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the carboxy acid group of Compound 172 and the side chains of R1047 and Q981; hydrogen bonding between the chromenone exocyclic ketone group of Compound 172, a bridging water molecule, and the side chain of H931; hydrogen bonding between the cyano group of Compound 172 and the side chain of Y1021; core pi-pi stacking between the chromenone core of Compound 172 and the side chain of F954; and pi-pi T-stacking between the 4-cyano-phenyl group of Compound 172 and the side chain of F909.

[55] Fig. 22. Graphic illustration of the interaction of PIK α _H1047R and Compound N3 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the carboxy acid group of Compound N3 and the side chains of R1047 and Q981; core pi-pi stacking between the chromenone core of Compound N3 and the side chain of F954 in addition to pi-pi T-stacking between the phenyl group of Compound N3 and the side chain of F954.

[56] Fig. 23. Graphic illustration of the interaction of PIK α _H1047R and Compound N4 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the carboxy acid group of Compound N4 and the side chains of R1047 and Q981; and hydrogen bonding between the chromenone exocyclic ketone group of Compound N4, a bridging water molecule, and the side chain of H931.

[57] Fig. 24. Graphic illustration of the interaction of PIK α _H1047R and Compound N5 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the carboxy acid group of Compound N5 and the side chains of R1047 and Q981; direct hydrogen bonding between

the isoxazole group of Compound N5 and side chain of H931; and core pi-pi stacking between the isoxazole core of Compound N5 and the side chain of F954.

[58] Fig. 25. Graphic illustration of the interaction of PIK α _M1043I_H1047R and Compound HP1 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the nitrogen atom in the isoindolin-1-one core of Compound HP1 and the carbonyl backbone group of D1018; core pi-pi stacking between the core of the 3-trifluoromethyl, 5-fluorophenyl group of Compound HP1 and the side chain of F937 in addition to pi-pi T-stacking between the core of the 3-trifluoromethyl, 5-fluorophenyl group of Compound HP1 and the side chain of F1002.

[59] Fig. 26. Graphic illustration of the interaction of PIK α _M1043I_H1047R and Compound HP2 based on an X-ray structure analysis. Interactions include direct hydrogen bonding between the nitrogen atom in the isoindolin-1-one core of Compound HP2 and the carbonyl backbone group of D1018; core pi-pi T-stacking between the core of the 3-trifluoromethyl, 5-fluorophenyl group of Compound HP2 and the side chain of F1002; and a chlorine-carbonyl interaction between the chlorine atom of the 2-chloro, 5-fluorophenyl group of Compound HP2 and the side chain carbonyl of E1012.

[60] Fig. 27. Graphic illustration of the interaction of PIK α _H1047R, Compound N6, and Compound HP2 in their respective allosteric pockets based on an X-ray structure analysis.

[61] Fig. 28. Effect of Compound 21 (37.5mg/kg), alpelisib (12.5 mg/kg), and fulvestrant(5mg/animal) in a T47D xenograft (H1047+/1, ER+, PR+, HER2-).

[62] Fig. 29. Effect of Compound 21 (37.5mg/kg), alpelisib (6.25mg/kg), and fulvestrant(5mg/animal) in a T47D xenograft (H1047+/1, ER+, PR+, HER2-).

[63] Fig. 30. Naïve and Compound 21 resistant MDA453 cells (having an M1043I 2nd site mutation) were treated with Compound 21, alpelisib, or Compound HP1.

[64] Fig. 31. Naïve and Engineered T47D Cells (having 6x M1043I 2nd site mutations) were treated with Compound 21, alpelisib, or Compound HP1.

[65] Fig. 32. Parental SUM185PE cells and Compound 21 resistant SUM185PE cells were treated with Compound 21, Compound 1, alpelisib, or Compound HP1

[66] Fig. 33. MDA453 naïve cells were treated with Compound 21 in combination with alpelisib.

- [67] Fig. 34. Synergy plot of MDA453 naïve cells treated with Compound 21 in combination with alpelisib.
- [68] Fig. 35. MDA453 naïve cells were treated with Compound 21 in combination with Compound HP1.
- [69] Fig. 36. Synergy plot of MDA453 naïve cells treated with Compound 21 in combination with Compound HP1.
- [70] Fig. 37. MDA453 naïve cells were treated with alpelisib in combination with Compound HP1.
- [71] Fig. 38. MDA453 naïve cells were treated with alpelisib in combination with Compound HP1.
- [72] Fig. 39. H1047R homozygous SUM185PE cells were treated with Compound 21 in combination with alpelisib.
- [73] Fig. 40. Compound 21 resistant SUM185PE cells treated with a combination of Compound 21 and alpelisib.
- [74] Fig. 41. H1047R homozygous SUM185PE cells were treated with Compound 21 in combination with Compound HP1.
- [75] Fig. 42. H1047R homozygous SUM185PE cells were treated with alpelisib in combination with Compound HP1.
- [76] Fig. 43. T47D cells treated with Compound 21 in combination with alpelisib.
- [77] Fig. 44. T47D cells treated with Compound 21 in combination with Compound HP1.
- [78] Fig. 45. T47D cells treated with alpelisib in combination with Compound HP1.
- [79] Fig. 46. T47D naïve cells treated with Compound 21 in combination with alpelisib.
- [80] Fig. 47. T47D 6x H1043I cells treated with Compound 21 in combination with alpelisib.
- [81] Fig. 48. Parental SUM185PE cells and Cpd-21-R SUM185PE cells treated with Compound 21, alpelisib, Compound HP1, Compound HP4, Compound HP5, or Compound HP6.
- [82] Fig. 49. T47D cells (5×H1047R/1×WT) or engineered T47D cells having 2nd site mutations (5×H1047R/6×C901F or 6×H1047R/M1043I) treated with Compound 21, alpelisib, Compound HP1, Compound HP4, Compound HP5, or Compound HP6.
- [83] Fig. 50. T47D cells treated with Compound 21 in combination with Compound HP6.
- [84] Fig. 51. T47D cells treated with Compound 21 in combination with Compound HP6.

[85] Fig. 52. Combination Index plot for Compound 21 in combination with Compound HP6 in T47D cells.

[86] Fig. 53. SUM185PE cells treated with Compound 21 in combination with Compound HP6.

[87] Fig. 54. Combination Index plot for Compound 21 in combination with Compound HP6 in SUM185PE cells.

[88] Fig. 55. T47D cells treated with Compound 21 in combination with Compound HP5.

[89] Fig. 56. Combination Index plot for Compound 21 in combination with Compound HP5 in T47D cells.

[90] Fig. 57. SUM185PE cells treated with Compound 21 in combination with Compound HP5.

[91] Fig. 58. Combination Index plot for Compound 21 in combination with Compound HP5 in SUM185PE cells.

Detailed Description

[92] The present invention provides methods of treating, preventing, or ameliorating a disease or disorder, or uses of PI3K inhibitors in the treatment, prevention, or amelioration of a disease or disorder, where the disease or disorder is dependent or associated with PI3K activity. In the disclosed methods and uses, a patient in need thereof is administered a therapeutically effective amount of a PI3K inhibitor or a combination of PI3K inhibitors, which may include allosteric inhibitors and orthosteric inhibitors. The methods and uses disclosed herein may be performed in the treatment of a variety of PI3K-dependent or PI3K-associated diseases, and disorders.

[93] In some embodiments of the disclosed methods and uses, the disease, or disorder is a cancer, such as breast cancer, brain cancers, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer. In some embodiments, the disease, or disorder associated with PI3K includes, but is not limited to, CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), endometrial cancer, breast cancer, esophageal squamous-cell cancer, cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma,

glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, and encapsulated glioma.

[94] The details of the invention are set forth in the accompanying description below. Although methods, and materials similar, or equivalent to those described herein can be used in the practice, or testing of the present disclosure, illustrative methods, and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description, and from the claims. In the specification, and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical, and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, and publications cited in this specification are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein.

Definitions

[95] The articles “a”, and “an” refer to one, or more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element, or more than one element.

[96] The term “and/or” means either “and”, or “or” unless indicated otherwise.

[97] The term “administer”, “administering”, or “administration” refers to either directly or indirectly administering to a patient a disclosed compound, or pharmaceutically acceptable salt of the disclosed compound, or a composition. “Administering” or “administration” may be performed by a caregiver, for example, by a medical professional or other caregiver where the medical professional or other caregiver administers to a patient a disclosed compound, or pharmaceutically

acceptable salt of the disclosed compound, or a composition. “Administering” or “administration” may be performed by a patient, for example, where a patient administers to themselves a disclosed compound, or pharmaceutically acceptable salt of the disclosed compound, or a composition.

[98] The term “alkenyl” refers to a straight, or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The “alkenyl” group contains at least one double bond in the chain. The double bond of an alkenyl group can be unconjugated, or conjugated to another unsaturated group.

Examples of alkenyl groups include ethenyl, propenyl, n-butenyl, iso-butenyl, pentenyl, or hexenyl.

[99] The term “alkoxy” refers to a straight, or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal “O” in the chain, *i.e.*, -O(alkyl). Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

[100] The term “alkyl” refers to a straight, or branched chain saturated hydrocarbon containing 1-12 carbon atoms, preferably 1-6 carbon atoms. Examples of a (C₁-C₆) alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and isohexyl.

[101] The term “alkynyl” refers to a straight, or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The “alkynyl” group contains at least one triple bond in the chain. Examples of alkynyl groups include ethynyl, propargyl, n-butylnyl, iso-butylnyl, pentynyl, or hexynyl.

[102] The term “aromatic” means a planar ring having $4n + 2$ electrons in a conjugated system. As used herein, “conjugated system” means a system of connected p-orbitals with delocalized electrons, and the system may include lone electron pairs.

[103] The term “aryl” unless otherwise specifically defined refers to cyclic, aromatic hydrocarbon groups that have 1 to 3 aromatic rings, including monocyclic, or bicyclic groups such as phenyl, biphenyl, or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). Furthermore, when containing two fused rings the aryl groups herein defined may have one, or more saturated, or partially unsaturated ring fused with a fully unsaturated aromatic ring. Exemplary ring systems of these aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl, phenalenyl, phenanthrenyl, indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

[104] The term “carrier” encompasses carriers, excipients, and diluents, and means a material, composition, or vehicle, such as a liquid, or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying, or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a patient.

[105] The term “cyano” means a substituent having a carbon atom joined to a nitrogen atom by a triple bond, i.e., $C\equiv N$.

[106] The term “cycloalkyl” means mono, or polycyclic saturated carbon rings containing 3-18 carbon atoms, preferably 3-10 carbon atoms. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, norbornyl, norbornenyl, bicyclo[2.2.2]octanyl, and bicyclo[2.2.2]octenyl.

[107] The term “disorder” means, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[108] The term “haloalkoxy” refers to an alkoxy group, as defined herein, which is substituted with one, or more halogen. Examples of haloalkoxy groups include, but are not limited to, trifluoromethoxy, difluoromethoxy, pentafluoroethoxy, and trichloromethoxy.

[109] The term “haloalkyl” refers to an alkyl group, as defined herein, which is substituted with one, or more halogen. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, and trichloromethyl.

[110] The term “halogen” or “halo” refers to fluorine, chlorine, bromine, or iodine.

[111] The term “heteroaryl” unless otherwise specifically defined means a monovalent monocyclic, or a polycyclic aromatic radical of 5 to 24 ring atoms, preferably 5 to 10 ring atoms, containing one, or more ring heteroatoms selected from N, O, S, P, or B, preferably 1, 2, 3, or 4 ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. A polycyclic aromatic radical includes two, or more fused rings, and may further include two, or more spiro-fused rings, e.g., bicyclic, tricyclic, tetracyclic, and the like. Unless otherwise specifically defined, “fused” means two rings sharing two ring atoms. Unless otherwise specifically defined, “spiro-fused” means two rings sharing one ring atom. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, O, S, P, or B, preferably N, O, or S. Heteroaryl as herein

defined also means a tricyclic heteroaromatic group containing one, or more ring heteroatoms selected from N, O, S, P, or B, preferably N, O, or S. Heteroaryl as herein defined also means a tetracyclic heteroaromatic group containing one, or more ring heteroatoms selected from N, O, S, P, or B, preferably N, O, or S. Examples of heteroaromatic groups include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuranyl, chromanyl, thiochromanyl, tetrahydroquinolyl, dihydrobenzothiazinyl, quinolyl, isoquinolyl, 1,6-naphthyridinyl, benzo[de]isoquinolyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydro pyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d]thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4]thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[1,5-a]pyridinyl, benzo[1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo[1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4-d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, and 3H-indolyl. Furthermore, when containing two, or more fused rings, the heteroaryl groups defined herein may have one, or more saturated, or partially unsaturated ring fused with one, or more fully unsaturated aromatic ring. In heteroaryl ring systems containing more than two fused rings, a saturated, or partially unsaturated ring may further be fused with a saturated, or partially unsaturated ring described herein. Furthermore, when containing three, or more fused rings, the heteroaryl groups defined herein may have one, or more saturated, or partially unsaturated ring spiro-fused. Any

saturated, or partially unsaturated ring described herein is optionally substituted with one, or more oxo. Exemplary ring systems of these heteroaryl groups include, for example, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, 3,4-dihydro-1H-isoquinolinyl, 2,3-dihydrobenzofuranyl, benzofuranonyl, oxindolyl, indolyl, 1,6-dihydro-7H-pyrazolo[3,4-c]pyridin-7-onyl, 7,8-dihydro-6H-pyrido[3,2-b]pyrroliziny, 8H-pyrido[3,2-b]pyrroliziny, 1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[4,3-e]pyridinyl, 7,8-dihydro-6H-pyrido[3,2-b]pyrroliziny, pyrazolo[1,5-a]pyrimidin-7(4H)-onyl, 3,4-dihydropyrazino[1,2-a]indol-1(2H)-onyl, benzo[c][1,2]oxaborol-1(3H)-olyl, 6,6a,7,8-tetrahydro-9H-pyrido[2,3-b]pyrrolo[1,2-d][1,4]oxazin-9-onyl, and 6a',7'-dihydro-6'H,9'H-spiro[cyclopropane-1,8'-pyrido[2,3-b]pyrrolo[1,2-d][1,4]oxazin]-9'-onyl.

[112] The term “heterocyclyl”, “heterocycle”, or “heterocycloalkyl” means mono, or polycyclic rings containing 3-24 atoms, preferably 3-10 atoms, which include carbon, and one, or more heteroatoms selected from N, O, S, P, or B, preferably 1, 2, 3, or 4 heteroatoms selected from N, O, and S, and wherein the rings are not aromatic. Examples of heterocyclyl rings include, but are not limited to, oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazoliny, oxazolidiny, thiazoliny, thiazolidiny, pyranyl, thiopyranyl, tetrahydropyranyl, dioxaliny, piperidinyl, morpholiny, thiomorpholiny, thiomorpholiny S-oxide, thiomorpholiny S-dioxide, piperazinyl, azepiny, oxepiny, diazepiny, tropanyl, oxazolidinonyl, and homotropanyl.

[113] The term “hydroxyalkyl” refers to an alkyl group, as defined herein, which is substituted with a hydroxy group.

[114] The term “in *cis*” when referring to two different mutations means that the two different mutations are located on the same chromosome.

[115] The term “isomers” refers to compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is

possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomers or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[116] The term “modulate”, “modulation”, or “modulating” refers to a biological activity of a compound, or substrate that inhibits and/or activates PI3K. Modulation may include inhibition.

[117] The terms “patient” and “subject” may be utilized interchangeably herein and mean a mammal such as a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon, or rhesus. Preferably, the mammal is human.

[118] The term “therapeutically effective amount” when used in connection with a compound refers to the amount or dose of the compound which upon single or multiple dose administration to the patient, provides the desired effect in the patient under diagnosis or treatment.

[119] An effective amount can be determined by one skilled in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount for a patient, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of patient; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[120] The term “treating” with regard to a patient, includes restraining, slowing, stopping, or reversing the progression or severity of an existing symptom or disorder. The term “treating” with regard to a patient, may include prescribing for a patient a therapeutic agent to be administered to the patient or a treatment regimen for the patient. The term “treating” with regard to a patient, may include ordering a diagnostic test for the patient. Diagnostic tests may include genomic analyses that identify mutations present in PI3K α , such as mutations in C901 (*e.g.*, C901F), M1043 (*e.g.*,

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M1043I/L), and/or H1047 (*e.g.*, H1047R) which mutations may be in *cis* (*i.e.*, on the same allele), as disclosed herein.

[121] The term “preventing” with regard to a patient, may mean preventing a disease or disorder and/or preventing a symptom of a disease or disorder. A patient in need thereof may include a patient at risk for developing a disease or disorder wherein the disclosed methods may performed in order to prevent the patient from developing the disease or disorder. A patient in need thereof may include a patient in remission wherein the disclosed methods may performed in order to prevent the disease or disorder from recurring in the patient.

[122] In regard to cancer, treating may mean administering a therapeutic agent to a patient and observing a decrease in tumor growth, a reduction in tumor size, and/or an increase in mean survival time for the patient after treatment.

[123] The term “PI3K” means “Phosphoinositide 3-Kinase.” The term “PI3K α ” means the Phosphoinositide 3-Kinase alpha, which is a Class I PI3K that comprises the PI3k, catalytic, alpha polypeptide (p110- α) encoded by the gene *PIK3CA*. The p110- α polypeptide alternatively may be referred to as “PIK3CA.” The p110- α polypeptide comprises 1068 amino acids and has the amino acid sequence of SEQ ID NO:1:

p110- α (SEQ ID NO:1)

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1      mpprpssgel wgihlmpri lvecllpngm ivtleclrea tlitikhelf kearkyplhq
61      llqdessyif vsvtgeaere effdetrrlc dlrlfqpfk viepvgnree kilnreigfa
121     igmpvcefdm vkdpevqdfn rnlnvckea vdlrdlnsph sramyvypn vesspelpkh
181     iynkldkgqi ivviwvivsp nndkqkytlk inhdcvpeqv iaeairkktr smllsseqlk
241     lcvleyggky ilkvvcgdey flekypslsq kyirscimlg rmpnlmlmak eslysqlipmd
301     cftmpsysrr istatpymng etstkslwvi nsalrikilc atyvvnvird idkiyvrtgi
361     yhggeplcdn vntqrvpcsn prwnewlnyd iyipdlpraa rlclsicsvk grkgakeehc
421     plawgninlf dytdtlvsgk malnlwpvph gledllnpig vtgsnpnket pclelefdwf
481     ssvvkfpdms vieehanwsv sreagfsysh aglsnrlard nelrendkeq lkaistrdpl
541     seiteqekdf lwshrhycvt ipeilpklll svkwnsrdev agmyclvkdw ppikpeqame
601     lldcnypdpm vrgfavrcle kyltddklsq yliqlvqvlk yeqyldnllv rflkkaltn

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661  qrighffffwh lksemhnktv sgrfgllles ycracgmylk hlnrqveame klinltdilk
721  gekkdetqkv qmkflveqmr rpdfmdalqg flsplnpahq lgnlrleecr imssakrplw
781  lnwenpdims ellfqneei fknqddlrqd mltlqiirim eniwqngld lrmlpygcls
841  igdcvgliev vrnshtimqi qckggkkgal qfnshtlhqw lkdknkgeiy daaidlftsr
901  cagycvatfi lgigdrhnsn imvkddgqlf hidfghfldh kkkkfgykre rvpfvltqdf
961  liviskgagc ctktreferf qemcykayla irqhanlfin lfsmmlgsgm pelqsfddia
1021 yirktlaldk teqealeyfm kqmdahhgg wttkmdwifh tikqhaln

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[124] The Enzyme Commission (EC) number for the catalytic activity of PI3K α is 2.7.1.153. The catalytic activity of PI3K α includes phosphatidylinositol-4,5-bisphosphate 3-kinase activity, whereby a phosphate group from adenosine triphosphate (ATP) is transferred to phosphatidylinositol-4,5-bisphosphate (PIP2) to create phosphatidylinositol-3,4,5-trisphosphate (PIP3). PI3K α catalyzes the addition of a 3-phosphate group from ATP to PIP2 by binding ATP in an ATP-binding pocket within the kinase catalytic domain in the p100 α subunit of PI3K α .

[125] The PI3K α inhibitors disclosed herein inhibit the phosphatidylinositol-4,5-bisphosphate 3-kinase activity of PI3K α . The disclosed inhibitors may inhibit PI3K α activity by binding at or near the ATP-binding pocket of PI3K α , which may be referred to as an “the PI3K α orthosteric pocket.” The disclosed inhibitors may prevent ATP from binding at the ATP-binding pocket as antagonists and/or the disclosed inhibitors may displace ATP from the ATP-binding pocket. The disclosed inhibitors may include orthosteric inhibitors that compete with ATP for binding at the ATP-binding site of PI3K α . The ATP-binding pocket of PI3K α has been studied and characterized via X-ray crystallography. (Gkeka et al., Exploring a Non-ATP Pocket for Potential Allosteric Modulation of PI3K α , J. Phys. Chem. B 2015, 119, 1002-1016, published Oct. 9, 2014; and Fairhurst et al., Identification and optimisation of 4,5-dihydrobenzo [1,2-d:3,4-d]bisthiazole and 4,5-dihydrothiazolo[4,5-h]quinazoline series of selective phosphatidylinositol-3 kinase alpha inhibitors, Biorg. & Medic. Chem. Lett. 25 (2015) 3575-3581, published June 26, 2015). The ATP-binding pocket is located in a cleft between the N-terminal and C-terminal lobes of the kinase catalytic domain of p100 α . The ATP-binding pocket may comprise one or more amino acid residues selected from R770, M772, P778, W780, I800, K802, D810, Y836, I848, V850, V851, S854, Q859, N920,

M922, F930, I932, and D933.

[126] Orthosteric inhibitors of PI3K α may bind to PI3K α at or near the ATP-binding pocket of PI3K α and may form interactions with one or more amino acids selected from R770, M772, P778, W780, I800, K802, D810, Y836, I848, V850, V851, S854, Q859, N920, M922, F930, I932, and D933. Interactions may include, but are not limited to hydrogen bonding either directly or via a bridging water molecule, pi-pi T-stacking, and coplanar core pi-pi stacking. Orthosteric inhibitors of PI3K α are known and may include, but are not limited to, alpelisib, inavolisib, and serabelisib, which are PI3K α selective inhibitors.

[127] The disclosed inhibitors may inhibit PI3K α by binding at or near a pocket of PI3K α which is not the ATP-binding pocket of PI3K α , which may be referred to as an “allosteric pocket.” The disclosed inhibitors may function as allosteric inhibitors of PI3K α . Allosteric inhibitors of PI3K α which may be utilized in the disclosed methods are disclosed in WO2021/202964 (Petra), WO2021/222556, WO2022/235574, WO2022/235575, WO2022/251482, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/056407, WO2023/060262, WO2023/288242, WO2023/081209, WO2023/081757, WO2023/081759, WO2023/078401, WO2023/104111, WO2023/109870, WO2023/159155, WO2023/168378, WO2023/173124, and WO2023/192416, and WO2023/288242, the contents of which are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein.

[128] In some aspects, the allosteric inhibitors disclosed herein may bind to PI3K α at or near an allosteric pocket of PI3K α referred to herein as “the PI3K α allosteric pocket 1.” In some aspects, allosteric inhibitors of PI3K α may bind the PI3K α allosteric pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. Interactions may include, but are not limited to hydrogen bonding either directly or via a bridging water molecule, pi-pi T-stacking, and coplanar core pi-pi stacking. Particular interactions may include one or more of the following interactions: direct hydrogen bonding between a carboxy acid group of the inhibitor and the side chains of R1047 and Q981; hydrogen bonding between a carboxy acid group of inhibitor, a bridging water molecule, and the side chain of Y985; hydrogen

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bonding between the chromenone exocyclic ketone group of the inhibitor, a bridging water molecule, and the side chain of H931; hydrogen bonding between the chromenone exocyclic ketone group of the inhibitor, a bridging water molecule, and the carbonyl backbone group of C901; hydrogen bonding between a cyano group of the inhibitor and the side chain of Y1021; core pi-pi stacking between the chromenone core of the inhibitor and the side chain of F954; pi-pi T-stacking between a phenyl core group of the inhibitor (e.g., a core in a substituent at position C2 of the chromenone core) and the side chain of F909; direct hydrogen bonding between a C3 substituent on the chromenone core of the inhibitor and side chain of H931; and core pi-pi stacking between a core of the inhibitor (e.g., a core in a substituent at position C3 of the chromenone core) and the side chain of F954. Allosteric inhibitors of PI3K α that bind to the PI3K α allosteric pocket 1 are disclosed in WO2021/202964, WO2022/235574, WO2022/235575, WO2022/251482, WO2023/056407, WO2023/060262, and WO2023/078401, the contents of which are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein.

[129] In some aspects, the allosteric inhibitors disclosed herein may bind to PI3K α at or near an allosteric pocket of PI3K α referred to herein as “the PI3K α allosteric pocket 2.” In some aspects, allosteric inhibitors of PI3K α may bind the PI3K α allosteric pocket 2 and may form an interaction with one or more amino acids selected from L911, F937, F1002, E1012, and D1018. Interactions may include, but are not limited to hydrogen bonding either directly or via a bridging water molecule, pi-pi T-stacking, and coplanar core pi-pi stacking. Particular interactions may include one or more of the following interactions: direct hydrogen bonding between the nitrogen atom in an isoindolin-1-one core of the inhibitor and the carbonyl backbone group of D1018; core pi-pi stacking between the core of a 3-trifluoromethyl, 5-fluorophenyl group of the inhibitor and the side chain of F937; pi-pi T-stacking between the core of a 3-trifluoromethyl, 5-fluorophenyl group of the inhibitor and the side chain of F1002; and a chlorine-carbonyl interaction between the chlorine atom of a 2-chloro, 5-fluorophenyl group of the compound and the side chain carbonyl of E1012.

[130] Allosteric inhibitors of PI3K α are disclosed in WO2021/222556, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/288242, WO2023/081757, and WO2023/081759, the

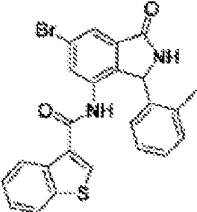
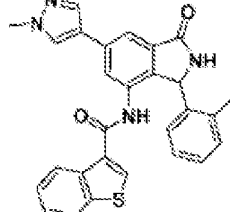
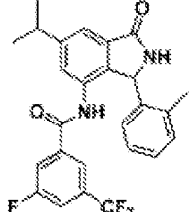
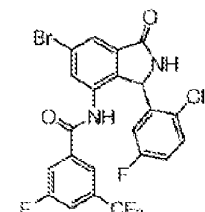
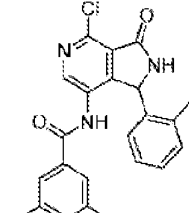
contents of which are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein. In some embodiments, the disclosed methods may utilize a PI3K α allosteric specific inhibitor disclosed in WO2021/222556, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/288242, WO2023/081757, or WO2023/081759, which optionally may bind to the PI3K α allosteric pocket 2.

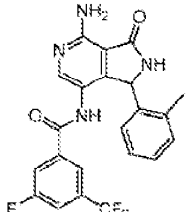
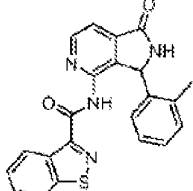
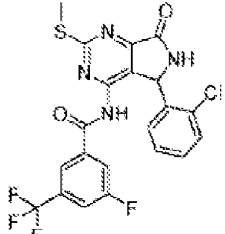
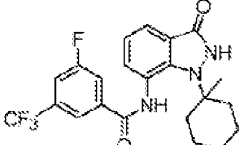
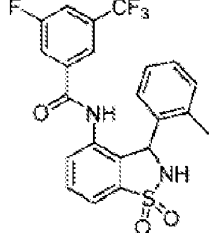
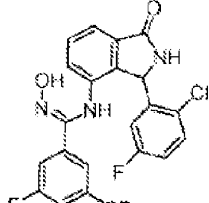
[131] In some embodiments of the methods disclosed herein, the methods may utilize a PI3K α allosteric specific inhibitor disclosed in WO2021/222556, at Table 1, pages 162-855, and referred to as Compounds I-1 through I-2704 or a pharmaceutically acceptable salt thereof.

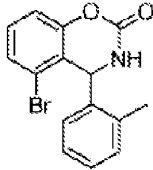
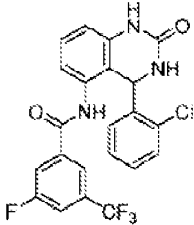
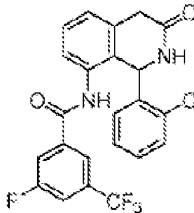
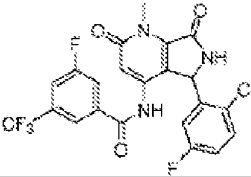
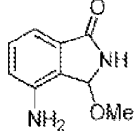
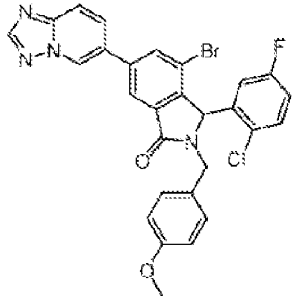
[132] In some embodiments, the methods may utilize a PI3K α allosteric specific inhibitor selected from:

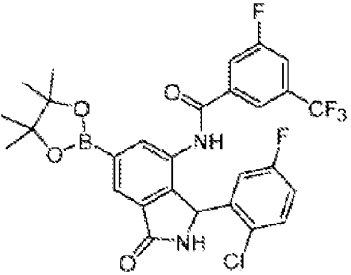
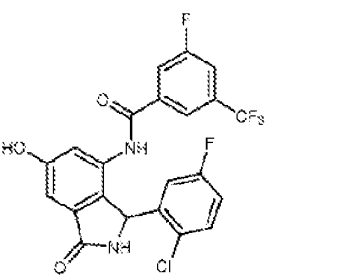
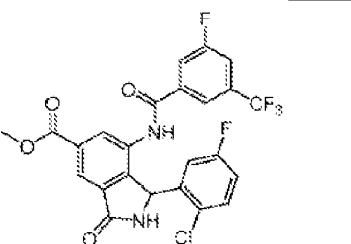
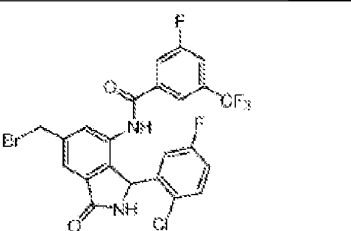
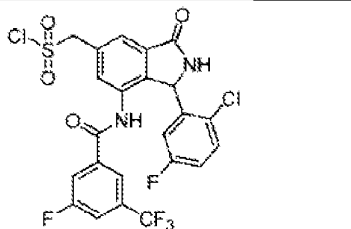
Compound Name	Structure
N-(1-Oxo-3-(o-tolyl)isoindolin-4-yl)benzo[b]thiophene-3-carboxamide (I-1)	
N-(1-Oxo-3-(o-tolyl)isoindolin-4-yl)bicyclo[2.2.2]octane-1-carboxamide (I-179)	
N-(1-Oxo-3-(o-tolyl)isoindolin-4-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxamide (I-328)	

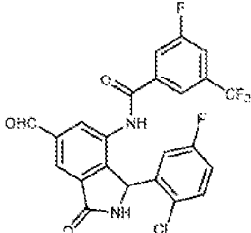
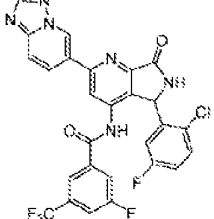
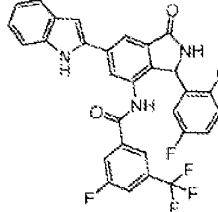
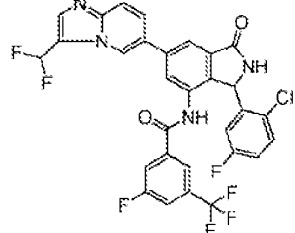
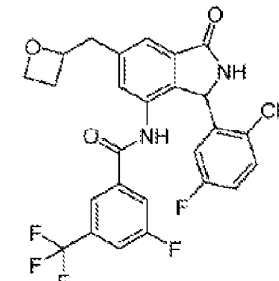
7-Chloro-N-[3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]imidazo[1,5-a]pyridine-1-carboxamide (I-258)	
7-Chloro-N-(1-oxo-3-(o-tolyl)isoindolin-4-yl)-3-methylimidazo[1,5-a]pyridine-1-carboxamide (I-277)	
6,8-Difluoro-N-(1-oxo-3-(o-tolyl)isoindolin-4-yl)imidazo[1,5-a]pyridine-3-carboxamide (I-180)	
N-(1-Oxo-3-(o-tolyl)isoindolin-4-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-1-carboxamide (I-226)	
N-(1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[d]isothiazole-3-carboxamide (I-13)	
N-[3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-2,3-dihydro-1H-indole-1-carboxamide (I-43)	

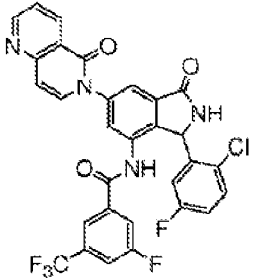
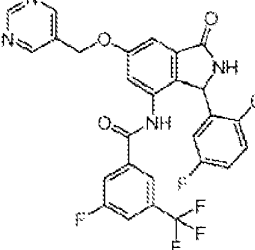
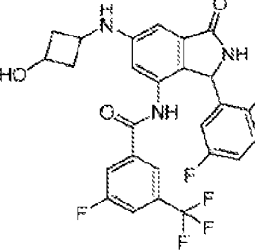
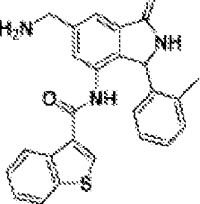
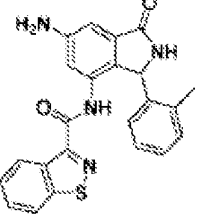
N-[6-bromo-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1-benzothiophene-3-carboxamide (I-29)	
N-[6-(1-methyl-1H-pyrazol-4-yl)-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1-benzothiophene-3-carboxamide (I-115)	
3-Fluoro-N-[3-(2-methylphenyl)-6-(isopropyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-5-(trifluoromethyl)benzamide (I-266)	
N-(6-Bromo-3-(2-chloro-5-fluorophenyl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
N-[4-Chloro-1-(2-methylphenyl)-3-oxo-1H,2H,3H-pyrrolo[3,4-c]pyridin-7-yl]-3-fluoro-5-(trifluoromethyl)benzamide (I-232)	

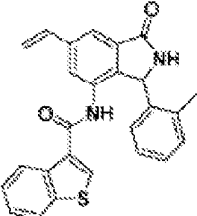
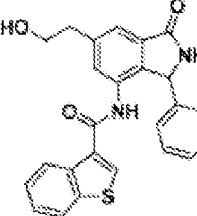
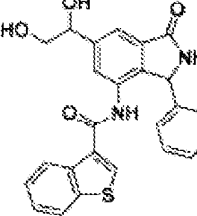
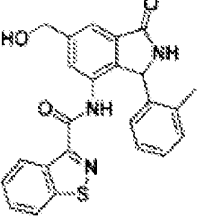
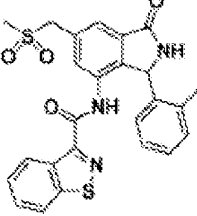
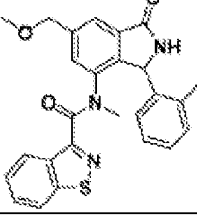
N-(4-Amino-3-oxo-1-(o-tolyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-262)	
N-[3-(2-Methylphenyl)-1-oxo-1H,2H,3H-pyrrolo[3,4-c]pyridin-4-yl]-1,2-benzothiazole-3-carboxamide (I-176)	
N-[5-(2-Chlorophenyl)-2-(methylsulfanyl)-7-oxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
3-Fluoro-N-[1-(1-methylcyclohexyl)-3-oxo-2,3-dihydro-1H-indazol-7-yl]-5-(trifluoromethyl)benzamide	
N-(1,1-Dioxido-3-(o-tolyl)-2,3-dihydrobenzo[d]isothiazol-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
(Z)-N-[3-(2-Chloro-5-fluorophenyl)-1-sulfanylidene-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-N'-hydroxy-5-(trifluoromethyl)benzimidamide	

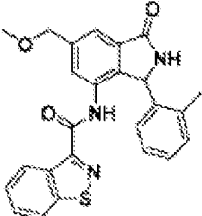
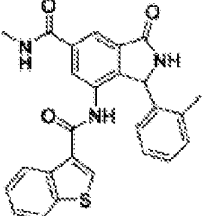
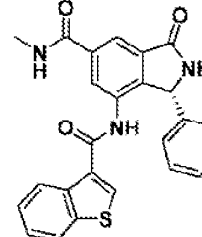
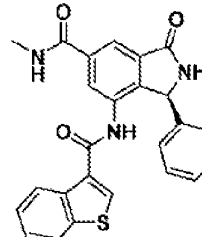
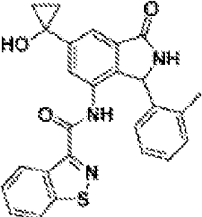
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N-(4-(2-Chlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-5-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
N-[1-(2-Chlorophenyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-8-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-[5-(2-Chloro-5-fluorophenyl)-1-methyl-2,7-dioxo-1H,2H,5H,6H,7H-pyrrolo[3,4-b]pyridin-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
4-Amino-3-methoxyisoindolin-1-one	
6-([1,2,4]Triazolo[1,5-a]pyridin-6-yl)-4-bromo-3-(2-chloro-5-fluorophenyl)-2-(4-methoxybenzyl)isoindolin-1-one	

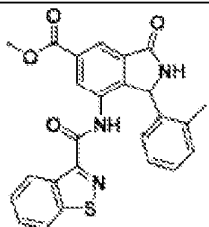
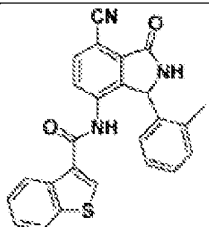
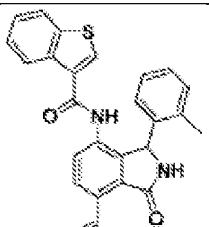
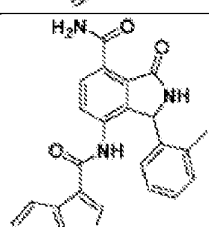
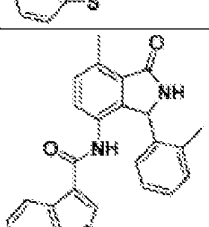
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N-(3-(2-Chloro-5-fluorophenyl)-6-hydroxy-1-oxoisoindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
Methyl 1-(2-chloro-5-fluorophenyl)-7-(3-fluoro-5-(trifluoromethyl)benzamido)-3-oxoisoindoline-5-carboxylate	
N-(6-(Bromomethyl)-3-(2-chloro-5-fluorophenyl)-1-oxoisoindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
(1-(2-Chloro-5-fluorophenyl)-7-(3-fluoro-5-(trifluoromethyl)benzamido)-3-oxoisoindolin-5-yl)methanesulfonyl chloride	

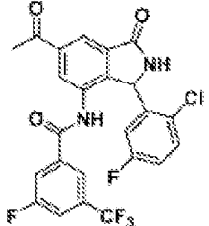
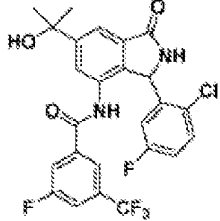
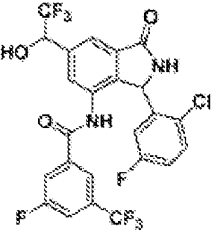
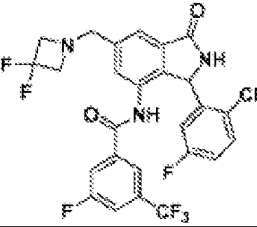
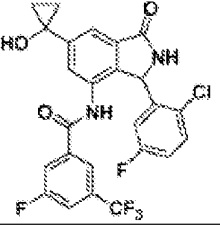
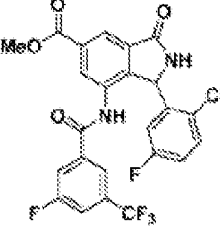
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N-(2-([1,2,4]Triazolo[1,5-a]pyridin-6-yl)-5-(2-chloro-5-fluorophenyl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide	
N-[3-(2-Chloro-5-fluorophenyl)-6-(1H-indol-2-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-[3-(2-Chloro-5-fluorophenyl)-6-[3-(difluoromethyl)imidazo[1,2-a]pyridin-6-yl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-[3-(2-Chloro-5-fluorophenyl)-6-[(oxetan-2-yl)methyl]-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	

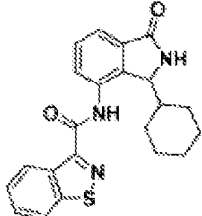
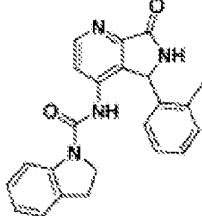
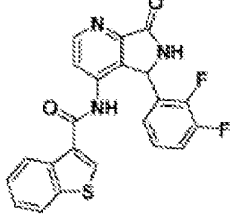
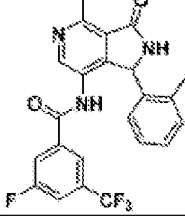
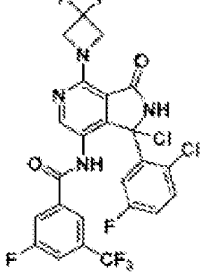
N-[3-(2-Chloro-5-fluorophenyl)-1-oxo-6-(5-oxo-5,6-dihydro-1,6-naphthyridin-6-yl)-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-[3-(2-Chloro-5-fluorophenyl)-1-oxo-6-[(pyrimidin-5-yl)methoxy]-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-[3-(2-Chloro-5-fluorophenyl)-1-oxo-6-{{[(1r*,3r**)3-hydroxycyclobutyl]amino}-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-(6-(Aminomethyl)-1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[b]thiophene-3-carboxamide (I-88)	
N-[6-Amino-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1,2-benzothiazole-3-carboxamide (I-50)	

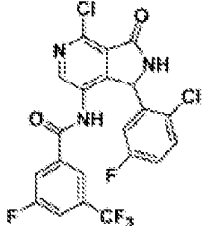
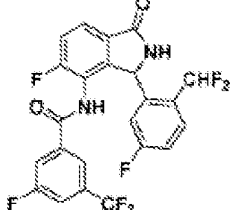
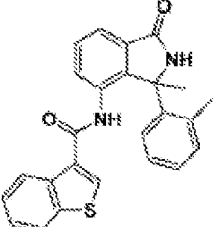
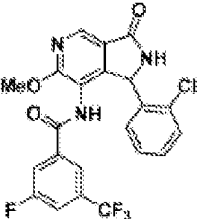
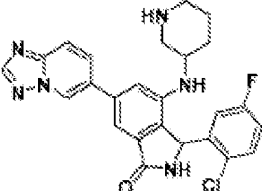
N-[6-Ethenyl-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1- benzothiophene-3-carboxamide (I-100)	
N-[6-(2-Hydroxyethyl)-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1- benzothiophene-3-carboxamide (I-181)	
N-[6-(1,2-Dihydroxyethyl)-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1- benzothiophene-3-carboxamide (I-139)	
N-[6-(Hydroxymethyl)-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1,2-benzothiazole-3-carboxamide (I-131)	
N-(6-((Methylsulfonyl)methyl)-1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[d]isothiazole-3-carboxamide (I-202)	
N-(6-(Methoxymethyl)-1-oxo-3-(o-tolyl)isoindolin-4-yl)-N-methylbenzo[d]isothiazole-3- carboxamide (I-134)	

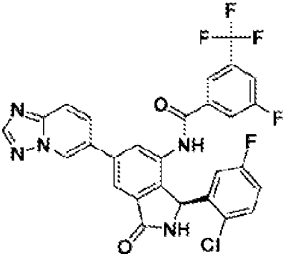
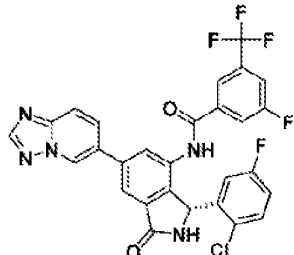
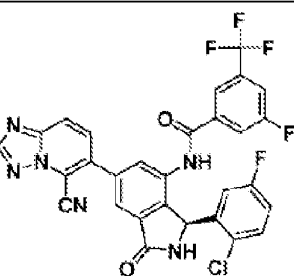
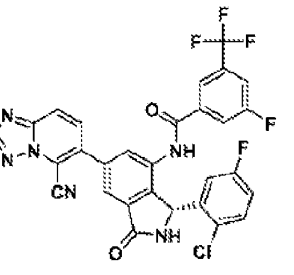
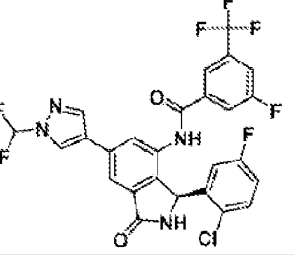
N-(6-(Methoxymethyl)-1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[d]isothiazole-3-carboxamide (I-146)	
7-(Benzo[b]thiophene-3-carboxamido)-N-methyl-3-oxo-1-(o-tolyl)isoindoline-5-carboxamide (I-6)	
(R)-7-(Benzo[b]thiophene-3-carboxamido)-N-methyl-3-oxo-1-(o-tolyl)isoindoline-5-carboxamide (I-75)	
(S)-7-(Benzo[b]thiophene-3-carboxamido)-N-methyl-3-oxo-1-(o-tolyl)isoindoline-5-carboxamide (I-76)	
N-[6-(1-hydroxycyclopropyl)-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1,2-benzothiazole-3-carboxamide (I-315)	

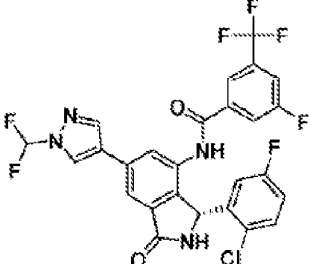
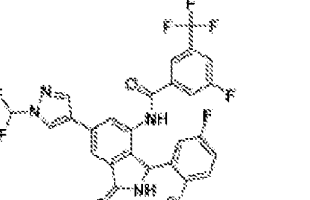
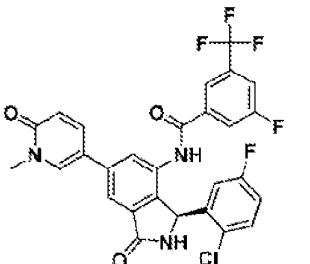
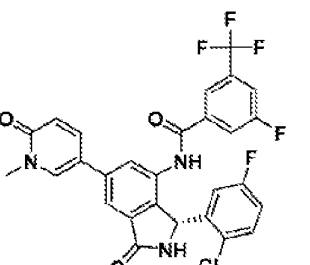
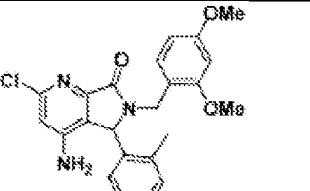
Methyl 7-(benzo[d]isothiazole-3-carboxamido)-3-oxo-1-(o-tolyl)isoindoline-5-carboxylate	
N-(7-Cyano-1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[b]thiophene-3-carboxamide (I-132)	
N-[7-Ethenyl-3-(2-methylphenyl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-1-benzothiophene-3-carboxamide (I-2157)	
7-(Benzo[b]thiophene-3-carboxamido)-3-oxo-1-(o-tolyl)isoindoline-4-carboxamide (I-149)	
N-(7-Methyl-1-oxo-3-(o-tolyl)isoindolin-4-yl)benzo[b]thiophene-3-carboxamide (I-153)	

N-(6-Acetyl-3-(2-chloro-5-fluorophenyl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-127)	
N-(3-(2-chloro-5-fluorophenyl)-6-(2-hydroxypropan-2-yl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-128)	
N-(3-(2-chloro-5-fluorophenyl)-1-oxo-6-(2,2,2-trifluoro-1-hydroxyethyl)isindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-270)	
N-(3-(2-Chloro-5-fluorophenyl)-6-((3,3-difluoroazetidin-1-yl)methyl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-348)	
N-[3-(2-chloro-5-fluorophenyl)-6-(1-hydroxycyclopropyl)-1-oxo-2,3-dihydro-1H-isindol-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (I-374)	
Methyl 1-(2-chloro-5-fluorophenyl)-7-[3-fluoro-5-(trifluoromethyl)benzamido]-3-oxo-2,3-dihydro-1H-isindole-5-carboxylate	

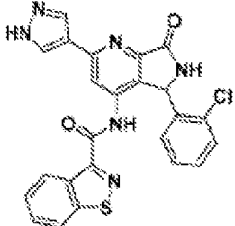
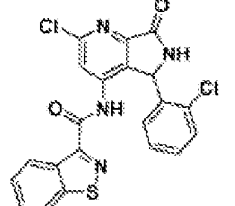
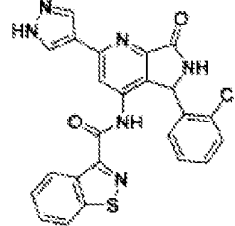
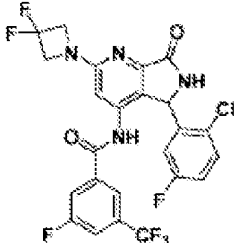
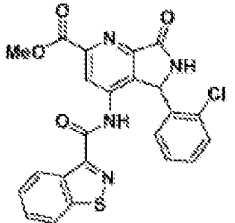
N-(3-Cyclohexyl-1-oxoisindolin-4-yl)benzo[d]isothiazole-3-carboxamide (I-204)	
N-(7-oxo-5-(o-tolyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)indoline-1-carboxamide (I-147)	
N-(5-(2,3-Difluorophenyl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)benzo[b]thiophene-3-carboxamide (I-15)	
3-Fluoro-N-(4-methyl-3-oxo-1-(o-tolyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-7-yl)-5-(trifluoromethyl)benzamide (I-244)	
N-(1-Chloro-1-(2-chloro-5-fluorophenyl)-4-(3,3-difluoroazetidin-1-yl)-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-274)	

N-[4-Chloro-1-(2-chloro-5-fluorophenyl)-3-oxo-1H,2H,3H-pyrrolo[3,4-c]pyridin-7-yl]-3-fluoro-5-(trifluoromethyl)benzamide	
N-(3-(2-(Difluoromethyl)-5-fluorophenyl)-5-fluoro-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-283)	
N-(3-Methyl-1-oxo-3-(o-tolyl)isindolin-4-yl)benzo[b]thiophene-3-carboxamide (I-80)	
N-(1-(2-chlorophenyl)-6-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-7-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-335)	
6-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(2-chloro-5-fluorophenyl)-4-(piperidin-3-ylamino)isindolin-1-one (I-2158)	

(S)-N-[3-(2-chloro-5-fluorophenyl)-1-oxo-6- {[1,2,4]triazolo[1,5-a]pyridin-6-yl}-2,3- dihydro-1H-isoindol-4-yl]-3-fluoro-5- (trifluoromethyl)benzamide (I-943)	
(R)- N-[3-(2-chloro-5-fluorophenyl)-1-oxo-6- {[1,2,4]triazolo[1,5-a]pyridin-6-yl}-2,3- dihydro-1H- isoindol-4-yl]-3-fluoro-5- (trifluoromethyl)benzamide (I-945)	
(S)-N-(3-(2-chloro-5-fluorophenyl)-6-(5-cyano-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-oxoisoindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-1647)	
(R)-N-(3-(2-chloro-5-fluorophenyl)-6-(5-cyano-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-oxoisoindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-1648)	
(S)-N-(3-(2-chloro-5-fluorophenyl)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1-oxoisoindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-1739)	

<p>(R)-N-(3-(2-chloro-5-fluorophenyl)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-1740)</p>	
<p>N-(3-(2-chloro-5-fluorophenyl)-6-(5-cyano-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide</p>	
<p>(S)-N-(3-(2-chloro-5-fluorophenyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-701)</p>	
<p>(R)-N-(3-(2-chloro-5-fluorophenyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-oxoisindolin-4-yl)-3-fluoro-5-(trifluoromethyl)benzamide (I-702)</p>	
<p>4-Amino-2-chloro-6-(2,4-dimethoxybenzyl)-5-(o-tolyl)-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one</p>	

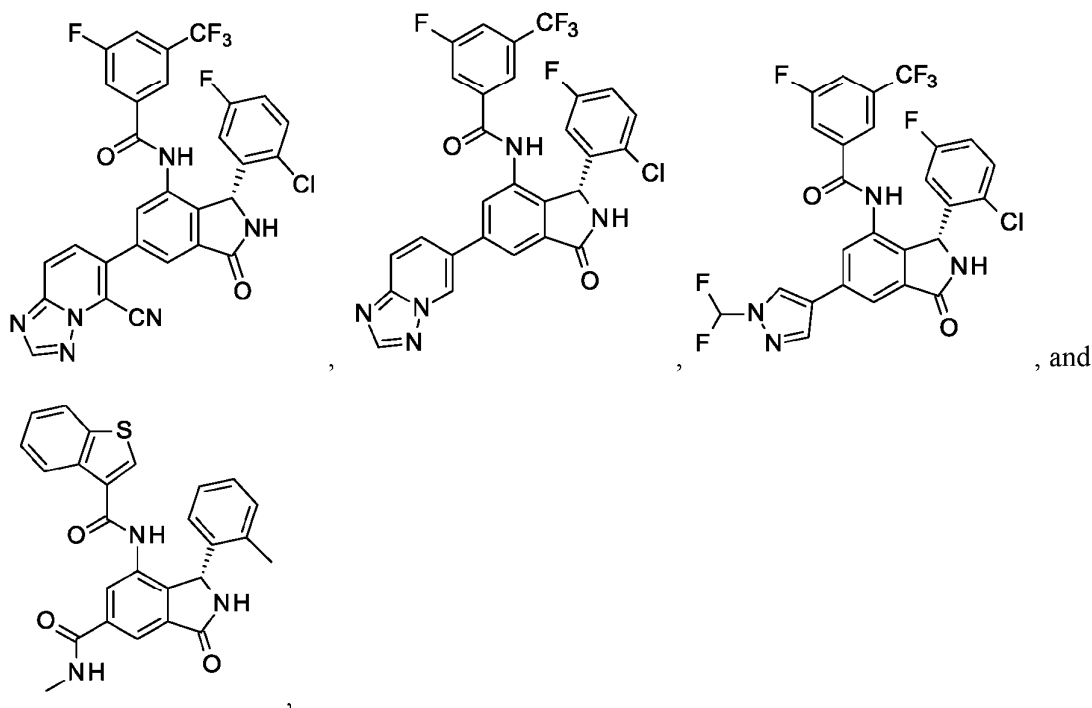
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N-(5-(2-Chlorophenyl)-7-oxo-2-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)benzo[d]isothiazole-3-carboxamide (I-94)	
N-[2-Chloro-5-(2-chlorophenyl)-7-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridin-4-yl]-1,2-benzothiazole-3-carboxamide (I-93)	
N-(5-(2-Chlorophenyl)-7-oxo-2-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-4-yl)benzo[d]isothiazole-3-carboxamide (I-94)	
N-[5-(2-Chloro-5-fluorophenyl)-2-(3,3-difluoroazetidin-1-yl)-7-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridin-4-yl]-3-fluoro-5-(trifluoromethyl)benzamide (I-286)	
Methyl 4-(1,2-benzothiazole-3-amido)-5-(2-chlorophenyl)-7-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridine-2-carboxylate (I-222)	

or a pharmaceutically acceptable salt thereof.

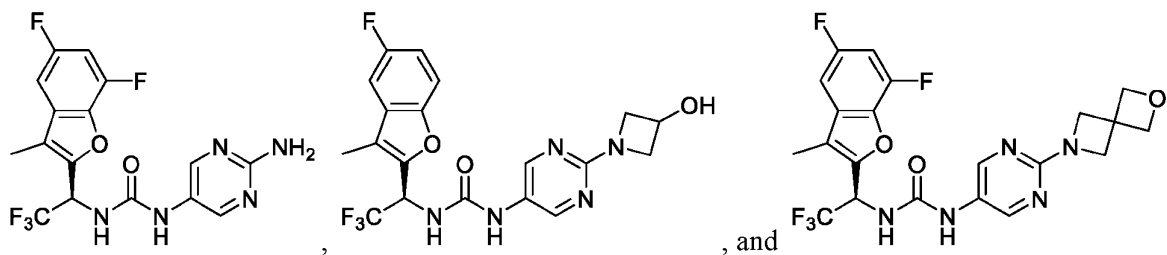
[133] In some embodiments, the methods may utilize a PI3K α allosteric specific inhibitor as disclosed in WO2021/222556, Table 1, selected from:

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or a pharmaceutically acceptable salt thereof.

[134] In some aspects of the methods disclosed herein, the methods may utilize a PI3K α allosteric specific inhibitor disclosed in WO2022/265993, at Tables A-D, pages 175-259. In some embodiments, the methods may utilize a PI3K α allosteric specific inhibitor disclosed in WO2022/265993 selected from:



or a pharmaceutically acceptable salt thereof.

[135] In some aspects, the PI3K α inhibitors utilized in the disclosed methods may bind to PI3K α concurrently. In some aspects, the disclosed combinations of inhibitors may bind to one or more

allosteric pockets (e.g., PI3K α allosteric pocket 1 and/or PI3K α allosteric pocket 2) and the disclosed combinations of inhibitors may bind to the PI3K α orthosteric pocket, concurrently. In some aspects, the disclosed combination of inhibitors may bind to a first allosteric pocket (e.g., one of PI3K α allosteric pocket 1 and PI3K α allosteric pocket 1) and the disclosed combinations of inhibitors may bind to a second allosteric pocket (e.g., the other of PI3K α allosteric pocket 1 and PI3K α allosteric pocket 2), concurrently. In some aspects, the disclosed combinations of inhibitors may bind to a first allosteric pocket (e.g., PI3K α allosteric pocket 1), the disclosed combinations of inhibitors may bind to a second or allosteric pocket (e.g., PI3K α allosteric pocket 2), and the disclosed combinations of inhibitors may bind to the PI3K α orthosteric pocket, concurrently.

[136] In some aspects, the PI3K α inhibitors utilized in the disclosed methods may bind to PI3K α competitively. In some aspects, the disclosed combinations of inhibitors bind to one or more allosteric pockets (e.g., PI3K α allosteric pocket 1 and/or PI3K α allosteric pocket 2) competitively.

[137] In some aspects, PI3K α selective inhibitors, which may include PI3K α selective allosteric inhibitors and PI3K α selective orthosteric inhibitors, may inhibit activity of PI3K α , such as phosphorylation activity of PI3K α . Phosphorylation activity may be assayed by methods including the methods disclosed herein. In some aspects, PI3K α selective inhibitors disclosed herein have an IC₅₀ in an *in vitro* phosphorylation assay which is less than about 100 nM, 50 nM, 10 nM, or 1 nM. In some aspects, PI3K α selective inhibitors disclosed herein have an EC₅₀ in an *in vitro* cell phosphorylation assay (e.g., a phosphorylation assay which measures phosphorylation of a substrate of PI3K α such as p-AKT, p-S6, or FOXM1) which is less than about 100 nM, 50 nM, 10 nM, or 1 nM. In some embodiments, PI3K α selective inhibitors, which may include PI3K α selective allosteric inhibitors and PI3K α selective orthosteric inhibitors, may inhibit the growth of cancer cells whose growth is dependent on PI3K α activity. Growth inhibition may be assayed using methods including methods disclosed herein including the use of cell titer glow reagents (CTGs). In some aspects, PI3K α selective inhibitors disclosed herein have an EC₅₀ in a growth inhibition assay which is less than about 100 nM, 50 nM, 10 nM, or 1 nM.

[138] In some aspects, the disclosed subject matter relates to methods of using multiple inhibitors of PI3K α or combinations of inhibitors of PI3K α for treating diseases and disorders associated with

PI3K α modulation. The term “multiple inhibitors of PI3K α ” or “combination of inhibitors of PI3K α ” as used herein, should be interpreted to mean “two or more different inhibitors of PI3K α .” The multiple inhibitors of PI3K α may inhibit PI3K α by binding at or near the same pocket of PI3K α (e.g., at or near an allosteric pocket of PI3K α), or the multiple inhibitors of PI3K α may inhibit PI3K α by binding at or near different pockets of PI3K α (e.g., where one inhibitor binds at or near an allosteric pocket of PI3K α and the other inhibitor binds at or near an orthosteric pocket of PI3K α , or where one inhibitor binds at or near an allosteric pocket of PI3K α and the other inhibitor binds at or near a different allosteric pocket of PI3K α).

[139] The disclosed methods may include administered a PI3K α selective inhibitor. A PI3K α selective inhibitor may be defined as an inhibitor of PI3K α which has an inhibitory activity for PI3K α which is greater than an inhibitory activity for one or more of PI3K β , PI3K γ , and PI3K δ . In some aspects, a PI3K α selective inhibitor may have an IC₅₀ value or an EC₅₀ value for PI3K α in a phosphorylation assay which is lower than an IC₅₀ value or an EC₅₀ value, respectively, for one or more of PI3K β , PI3K γ , and PI3K δ in the phosphorylation assay. Suitable phosphorylation assays for determining IC₅₀ values for PI3K α , PI3K β , PI3K γ , and PI3K δ , may include, but are not limited to *in vitro* biochemical or cell-based phosphorylation assays. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for PI3K α in a phosphorylation assay which is less than about 100 nM, 50 nM, 10 nM, or 1 nM. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for one or more of PI3K β , PI3K γ , and PI3K δ in a phosphorylation assay which is greater than about 100 nM, 200 nM, 500 nM, or 1000 nM. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for PI3K α in a phosphorylation assay which is at least 5 $\times$, 10 $\times$, 20 $\times$, 30 $\times$, 40 $\times$, 50 $\times$, 100 $\times$, 500 $\times$, or 1000 $\times$ less than an IC₅₀ value or an EC₅₀ value, respectively, for one or more of PI3K β , PI3K γ , and PI3K δ in the phosphorylation assay.

[140] The disclosed PI3K α selective inhibitors may exhibit selectivity for mutant forms of PI3K α relative to wild-type forms of PI3K α . In some aspects, the disclosed PI3K α selective inhibitors may exhibit selectivity for H1047R mutant PI3K α relative to wild-type PI3K α . In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for H1047R mutant PI3K α in a phosphorylation assay which is less than an IC₅₀ value or an EC₅₀ value, respectively for wild-type

PI3K α in the phosphorylation assay. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for H1047R mutant PI3K α in a phosphorylation assay which is less than about 100 nM, 50 nM, 10 nM, or 1 nM. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for wild-type PI3K α in a phosphorylation assay which is greater than about 100 nM, 200 nM, 500 nM, or 1000 nM. In some aspects, a PI3K α selective inhibitor has an IC₅₀ value or an EC₅₀ value for H1047R mutant PI3K α in a phosphorylation assay which is at least 5 $\times$, 10 $\times$, 20 $\times$, 30 $\times$, 40 $\times$, 50 $\times$, 100 $\times$, 500 $\times$, or 1000 $\times$ less than an IC₅₀ value or an EC₅₀ value for wild-type PI3K α in the phosphorylation assay. Suitable phosphorylation assays for determining IC₅₀ values or EC₅₀ values for H1047R mutant PI3K α relative to wild-type PI3K α , may include, but are not limited to *in vitro* biochemical or cell-based phosphorylation assays.

[141] The methods disclosed herein may recite a “first PI3K α selective inhibitor” and a “second PI3K α selective inhibitor.” This should not be interpreted as requiring that the first PI3K α selective inhibitor is administered prior (e.g., temporally) to the second PI3K α selective inhibitor in the disclosed methods. In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor may be administered simultaneously or substantially simultaneously (e.g. within less than about 12, 6, 2, 1, 0.5, 0.25, or 0.1 hours of each other), separately or at substantially different times (e.g., more than 12, 24, 48, or 72 hours apart, or more than 1, 2, 3, or 4 weeks apart, or more than 1, 2, 3, or 4 months apart), or sequentially (e.g., where the first PI3K α selective inhibitor is administered before the second PI3K α selective inhibitor, or where the second PI3K α selective inhibitor is administered before the first PI3K α selective inhibitor).

[142] In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor may be administered by the same actor. In some aspects, a caretaker (e.g., a patient’s physician or a patient’s non-physician caretaker) administers both of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor to the patient. In some aspects, a patient administers both of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor to themselves. In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor may be administered by separate actors. In some aspects, a caretaker administers one of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor, and a different

caretaker administers the other of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor. In some aspects, a caretaker administers one of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor to the patient, and a patient administers the other of the first PI3K α selective inhibitor and the second PI3K α selective inhibitor to themselves.

[143] In some aspects of the disclosed methods, the therapeutically effective amount of the PI3K α selective inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. Adverse events may include, but are not limited to hyperglycemia, which may be defined as blood glucose greater than about 100, 105, 110, 115, 120, or 125 mg/dL while fasting (e.g., after not eating for at least 8 hours), or blood glucose greater than about 155, 160, 165, 170, 175, or 180 mg/dL one to two hours after eating. Adverse events may include but are not limited to hyperinsulinemia, diarrhea, dehydration, skin rash, lymphopenia, Increased alanine transaminase, fatigue, anemia, elevated serum lipase, anorexia, stomatitis, vomiting, weight loss, hypocalcemia, hypoglycemic disorder, alopecia, prolonged activated partial thromboplastin time, kidney disease with reduction in glomerular filtration rate (GFR), acute abdominal pain, and abnormal hepatic function tests.

[144] In some aspects of the disclosed methods, a therapeutically effective amount of a PI3K α selective inhibitor is administered to the patient in need thereof, and the PI3K α selective inhibitor functions as an allosteric inhibitor. In some aspects, the therapeutically effective amount of a PI3K α selective allosteric inhibitor administered to the patient is a 100-1200 mg oral dose (e.g., BID (administered two times daily)). In some aspects, the therapeutically effective amount of the first allosteric inhibitor administered to the patient is 9-75 mg/kg oral dose (e.g., 37.5 mg/kg oral dose BID).

[145] The PI3K α selective allosteric inhibitors disclosed herein, or a pharmaceutically acceptable salts thereof, and the one or more additional therapeutic agents and their respective pharmaceutically acceptable salts are generally effective over a wide dosage range. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual

patient, and the severity of the patient's symptoms.

[146] In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 200 mg to 2400 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 400 mg to 2000 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 600 mg to 1200 mg.

[147] In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 200 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 300 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 400 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 500 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 600 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 700 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 800 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 900 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1000 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1100 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1200 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1300 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1400 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1500 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is

administered at a total daily dose of 1600 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1700 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1800 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1900 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2000 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2100 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2200 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2300 mg. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2400 mg.

[148] In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 200 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 300 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 400 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 500 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 600 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 700 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 800 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 900 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1000 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a

pharmaceutically salt thereof, is administered at a total daily dose of 1100 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1200 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1300 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1400 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1500 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1600 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1700 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1800 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 1900 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2000 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2100 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2200 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2300 mg in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a total daily dose of 2400 mg in a 28-day cycle.

[149] In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 100 mg to 1200 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 200 mg to 1000 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 300 mg to 600 mg twice a day.

[illegible]

administered at a dose of 1000 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1050 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1100 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1150 mg twice a day. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1200 mg twice a day.

[151] In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 100 mg to 1200 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 200 mg to 1000 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 100 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 200 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 150 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 200 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 250 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 300 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 350 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 400 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 450 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 500 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is

administered at a dose of 550 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 600 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 650 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 700 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 750 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 800 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 850 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 900 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 950 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1000 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1050 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1100 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1150 mg twice a day in a 28-day cycle. In an embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1200 mg twice a day in a 28-day cycle.

[152] In a preferred embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 200 mg twice a day in a 28-day cycle. In another preferred embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 400 mg twice a day in a 28-day cycle. In another preferred embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of

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600 mg twice a day in a 28-day cycle. In another preferred embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 800 mg twice a day in a 28-day cycle. In another preferred embodiment, a PI3K α selective allosteric inhibitor, or a pharmaceutically salt thereof, is administered at a dose of 1000 mg twice a day in a 28-day cycle.

[153] In some aspects, the therapeutically effective amount of the a PI3K α selective allosteric inhibitor administered to the patient is a 9, 15, 20, 25, 30, 35, 37.5, 40, 45, 50, 55, 60, 65, 70, or 75 mg/kg oral dose (e.g., QD or BID), or a dose within a range bounded by any of these values. In some aspects, the therapeutically effective amount of the a PI3K α selective allosteric inhibitor administered to the patient is a 9-75 mg/kg oral dose (e.g., QD or BID 37.5 mg/kg). In some aspects, the therapeutically effective amount of the a PI3K α selective allosteric inhibitor administered to the patient is less than about 75, 70, 65, 60, 55, 50, 45, 40, 37.5, 30, 35, 30, 25, 30 15, 9, 8, 7, 6, or 5 mg/kg oral dose (e.g., QD or BID).

[154] In some aspects of the disclosed methods, a therapeutically effective amount of a PI3K α selective inhibitor is administered to the patient in need thereof, and the PI3K α selective inhibitor functions as an orthosteric inhibitor. In some aspects, the therapeutically effective amount of the PI3K α selective orthosteric inhibitor administered to the patient is a 300 mg oral dose QD (i.e., administered once a day) or less than about a 300 mg oral dose QD, such as less than about 250, 200, 150, 100, or 50 mg QD. In some aspects, the therapeutically effective amount of the PI3K α selective orthosteric inhibitor administered to the patient is a 50 mg/kg oral dose QD (i.e., administered once a day) or less than about a 50 mg/kg oral dose QD, such as less than about 30, 12.5, 6.25, or 3.125 mg/kg oral dose QD, for example when the PI3K α selective orthosteric inhibitor is administered with a PI3K α selective allosteric inhibitor (e.g., a PI3K α selective allosteric inhibitor that binds the PI3K α allosteric pocket 1 or the PI3K α allosteric pocket 2), simultaneously, separately, or sequentially.

[155] The disclosed methods may relate to treating a patient having a disease or disorder which is resistant to treatment with a PI3K α selective inhibitor. Resistance may include “acquired resistance” where a patient has a disease or disorder which has developed resistance to treatment with the PI3K α selective inhibitor after having been treated previously with the PI3K α selective inhibitor.

Resistance may include “*de novo* resistance” where a patient has a disease or disorder that is resistant to treatment with the PI3K α selective inhibitor and the patient was not treated previously with the PI3K α selective inhibitor.

[156] The disclosed methods may relate to a patient having a disease or disorder which has acquired resistance to a PI3K α selective inhibitor. Acquired resistance may be characterized *in vitro* by methods that include, but are not limited to: an EC₅₀ shift in growth inhibition, for example as measured by a cell viability assay; changes in phosphorylation inhibition, for example as assayed by Western blot and quantification of phosphorylated bands, or as assayed by determining an IC₅₀ value in a phosphorylation assay; and stability of cell colonies in a selection-free condition. Acquired resistance may be characterized *in vivo* or clinically by observing recurrence in a patient after the patient was treated with the PI3K α selective inhibitor and the patient previously exhibited remission. For a patient having cancer, acquired resistance may be characterized clinically by observing recurrence after having previously observed remission in the patient when the patient was treated with the PI3K α selective inhibitor. For a patient having cancer, acquired resistance may be characterized clinically by observing an increase in growth of cancer after having previously observed a decline in growth of the cancer after treatment with the PI3K α selective inhibitor. For a patient having cancer, acquired resistance may be characterized clinically by observing recurrence of the cancer in a different part of the patient’s body than where the cancer was first observed prior to treatment with the PI3K α selective inhibitor.

[157] In the disclosed methods, a patient may be administered a therapeutically effective amount of one or more PI3K α selective inhibitors, which may include a combination of allosteric inhibitors and/or orthosteric inhibitors. In some aspects, the disclosed methods further comprise administering to the patient a therapeutically effective amount of another therapeutic agent. In some aspects of the disclosed methods, the patient further is administered a therapeutically effective amount of a selective estrogen receptor degrader (SERD). Suitable SERDs may include, but are not limited to imlunestrant, fulvestrant, giredestrant, amcenestrant, rintodestrant, elacestrant, camizestrant, LSZ102, Zn-c5, and D-0502. In some aspects of the disclosed methods, the therapeutically effective amount of the SERD is a dose of 500 mg, which may be administered on days 1, 15, and 29 or a

treatment regimen.

[158] In the disclosed methods, a patient in need thereof may have cancer. In some aspects, the patient in need thereof may have breast cancer. In some aspects, the patient in need thereof may have PIK3CA-mutated, advanced, or metastatic breast cancer. PIK3CA-mutated cancer may include cancer having one or more mutations selected from, but not limited to E542K, E545K, E453Q/K, E726K, C901F, M1043I/L, and H1047R, optionally wherein the one or more mutations are in *cis* (i.e., on the same allele). In some aspects, the patient in need thereof may have PIK3CACA H1047R-mutant advanced, or metastatic breast cancer which is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[159] In some aspects of the disclosed methods, the patient in need thereof is a postmenopausal female.

[160] In some aspects of the disclosed methods, the patient has type II diabetes mellitus.

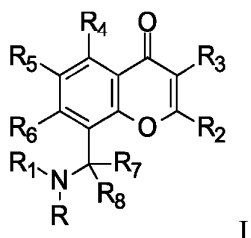
[161] I.A. Use of a Combination of an Allosteric Inhibitor and an Orthosteric Inhibitor of Phosphoinositide 3-Kinase (PI3K) for Treating Diseases and Disorders Associated with PI3K Modulation

[162] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α . The methods may comprise administering to a patient in need thereof: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds to the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to the PI3K α orthosteric pocket. The disclosed methods may comprise administering a first PI3K α selective inhibitor which is a PI3K α selective allosteric inhibitor and a second PI3K α selective inhibitor which is a PI3K α selective orthosteric inhibitor. In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor may be administered simultaneously, separately, or sequentially.

[163] In some aspects of the disclosed methods, the first PI3K α selective inhibitor is an allosteric

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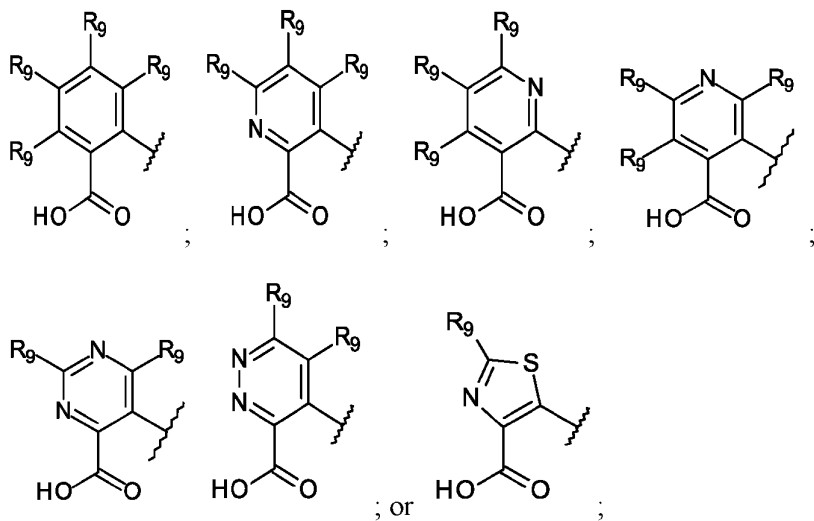
inhibitor of a Formula I:



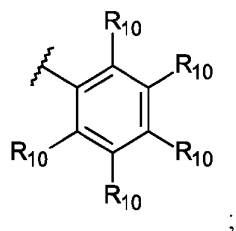
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted

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heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

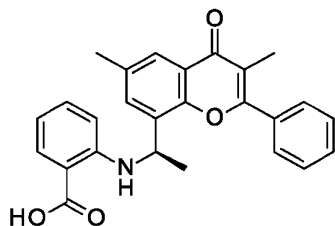
R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[164] In some aspects of the disclosed methods, the allosteric inhibitor is of a formula:

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or a pharmaceutically acceptable salt thereof.

[165] The second PI3K α selective inhibitor utilized in the disclosed methods binds to the PI3K α orthosteric pocket and may function as an orthosteric inhibitor. In some aspects, the orthosteric inhibitor is alpelisib or a pharmaceutically acceptable salt thereof. In some aspects, the orthosteric inhibitor is inavolisib or a pharmaceutically acceptable salt thereof. In some aspects, the orthosteric inhibitor is serabelisib or a pharmaceutically acceptable salt thereof.

[166] In some aspects of the disclosed methods, a therapeutically effective amount of the first PI3K α selective inhibitor is administered to the patient in need thereof, and the first PI3K α selective inhibitor functions as an allosteric inhibitor. In some aspects, the therapeutically effective amount of the allosteric inhibitor administered to the patient is a 100-1200 mg oral dose BID (i.e., administered two times daily). In some aspects, the therapeutically effective amount of the allosteric inhibitor administered to the patient is 9-75 mg/kg oral dose BID (e.g., 37.5 mg/kg or less than about 37 mg/kg).

[167] In some aspects of the disclosed methods, a therapeutically effective amount of the second PI3K α selective inhibitor administered to the patient in need thereof, and the PI3K α selective inhibitor functions as an orthosteric inhibitor. In some aspects, the therapeutically effective amount of the orthosteric inhibitor administered to the patient is a 300 mg oral dose QD (i.e., administered once a day) or less than about a 300 mg oral dose QD.

[168] In some aspects of the disclosed methods, a synergistic effect may be observed after administering a therapeutically effective amount of the allosteric inhibitor and a therapeutically effective amount of the orthosteric inhibitor. In some aspects of the disclosed methods, the therapeutically effective amount of the allosteric inhibitor administered to the patient may be less than a therapeutically effective amount of the allosteric inhibitor that is required in a treatment

method where the orthosteric inhibitor is not administered. In some aspects of the disclosed methods, the therapeutically effective amount of the orthosteric inhibitor that is administered to the patient may be less than a therapeutically effective amount of the orthosteric inhibitor that is required in a treatment method where the allosteric inhibitor is not administered.

[169] In some aspects of the disclosed methods, the therapeutically effective amount of the allosteric inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. In some aspects of the disclosed methods, the therapeutically effective amount of the orthosteric inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events.

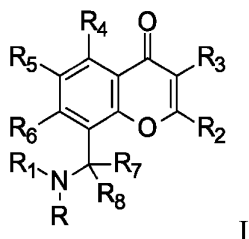
[170] In some aspects of the disclosed methods, the allosteric inhibitor and the orthosteric inhibitor are administered simultaneously, separately, or sequentially. In some aspects of the disclosed methods, the allosteric inhibitor and the orthosteric inhibitor are administered simultaneously or substantially simultaneously. In some aspects of the disclosed methods, the dose of the orthosteric inhibitor which is administered to the patient is less than about 50, 30, 12.5, 6.25, or 3.125 mg/kg oral dose QD, optionally where the orthosteric inhibitor is alpelisib.

[171] In the disclosed methods, the first PI3K α selective inhibitor and the second PI3K α selective inhibitor may be administered sequentially. In some aspects, the methods comprise administering the second PI3K α selective inhibitor after the disease or disorder has developed resistance to the first PI3K α selective inhibitor. In some aspects, the second PI3K α selective inhibitor is administered initially after the disease or disorder has developed resistance to the first PI3K α selective inhibitor. In some aspects, the second PI3K α selective inhibitor is not administered until after the disease or disorder has developed resistance to the first PI3K α selective inhibitor. In some aspects, resistance is characterized by occurrence of a M1043 mutation (e.g., M1043I or M1043L) and/or a C901 mutation (e.g., C901F). A patient exhibiting resistance may have a disease or disorder comprising the M1043I/L mutation and/or the C901F mutation together with the H1047R mutation (optionally wherein the M1043I/L mutation and the C901F mutation are in *cis* on the same allele with the H1047R mutation).

[172] I.B. Use of a Combination of a First Allosteric Inhibitor and a Second Allosteric Inhibitor of Phosphoinositide 3-Kinase (PI3K) for Treating Diseases and Disorders Associated with PI3K Modulation, Where the First Allosteric Inhibitor and the Second Allosteric Inhibitor Bind to Different Allosteric Pockets

[173] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof. The methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds to the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047; and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to a different allosteric pocket of PI3K α , such as the PI3K α allosteric pocket 2, and the second PI3K α selective inhibitor optionally may form an interaction with one or more amino acids selected from L911, F937, F1002, E1012, and D1018. The disclosed methods may comprise administering a PI3K α selective allosteric inhibitor (i.e., a first allosteric inhibitor) and a different PI3K α selective allosteric inhibitor (i.e., a second allosteric inhibitor), where the first allosteric inhibitor and the second allosteric inhibitor bind to different allosteric pockets (e.g., the PI3K α allosteric pocket 1 and the PI3K α allosteric pocket 2, respectively), and the first allosteric inhibitor and the second allosteric inhibitor are administered simultaneously, separately, or sequentially.

[174] In the disclosed methods, the first PI3K α selective inhibitor may be an allosteric inhibitor of a Formula I:

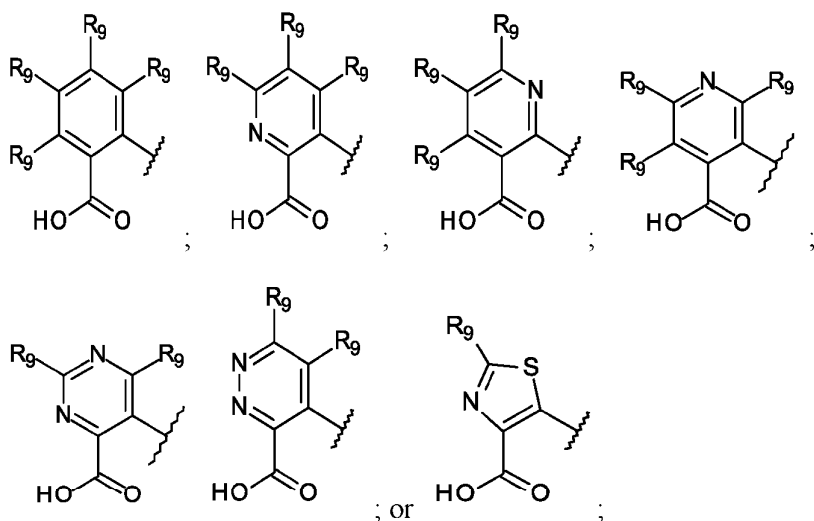


or pharmaceutically acceptable salt thereof, wherein:

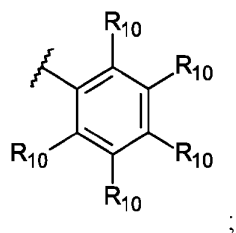
- 63 -

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

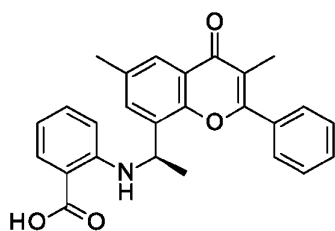
- 64 -

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[175] In some aspects of the disclosed methods, the first PI3K α selective inhibitor is an allosteric inhibitor of a formula:



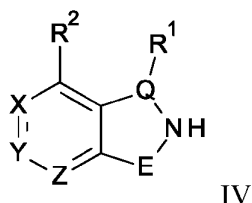
or a pharmaceutically acceptable salt thereof.

[176] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor disclosed in WO2021/222556, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/288242, WO2023/081757, or WO2023/081759, the contents of which are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of

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making and using the PI3K α inhibitor compounds disclosed therein.

[177] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor of a Formula IV:



or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)₂-, -C(R^E)₂C(R^E)₂-, -C(S)-, -S(O)₂-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)₂C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R¹ is -L¹-R^{1A};

R² is -L²-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R¹ are taken together with their intervening atoms to form a 4-8 membered saturated or

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partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C} ;

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC} ; each of L^1 , L^2 , L^E , L^Q , L^X , L^Y , and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, $-N(R)-$, $-N(R)C(O)-$, $-N(R)C(NR)-$, $-N(R)C(NOR)-$, $-N(R)C(NCN)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C} ;

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$; each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially

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unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

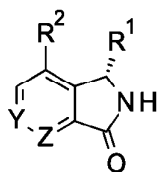
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

[178] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor of a Formula XXVIII:

[179]

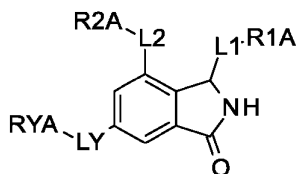
- 68 -



[180] XXVIII

[181] or a pharmaceutically acceptable salt thereof.

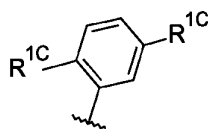
[182] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor of a Formula:



[183]

[184] or a pharmaceutically acceptable salt thereof.

[185] In some aspects, the second PI3K α selective inhibitor is of a formula in which



[186] R¹ is

[187] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R¹C is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[188] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R¹C is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[189] In some aspects, the second PI3K α selective inhibitor is of a formula in which R² is -

N(H)C(O)-R²A, -N(H)C(O)N(H)-R²A, -C(O)N(H)-R²A, -N(H)-R²A, -S(O)₂CH₂-R²A, -CH₂S(O)₂-R²A, or -C(H)(CH₃)OH.

[190] In some aspects, the second PI3K α selective inhibitor is of a formula in which R²A is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

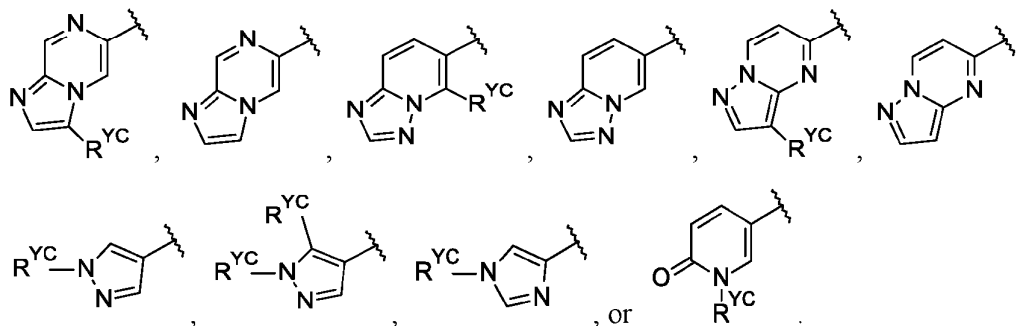
- 69 -

[191] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{2C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[192] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{2C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[193] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r⁶ instances of R^{YC}.

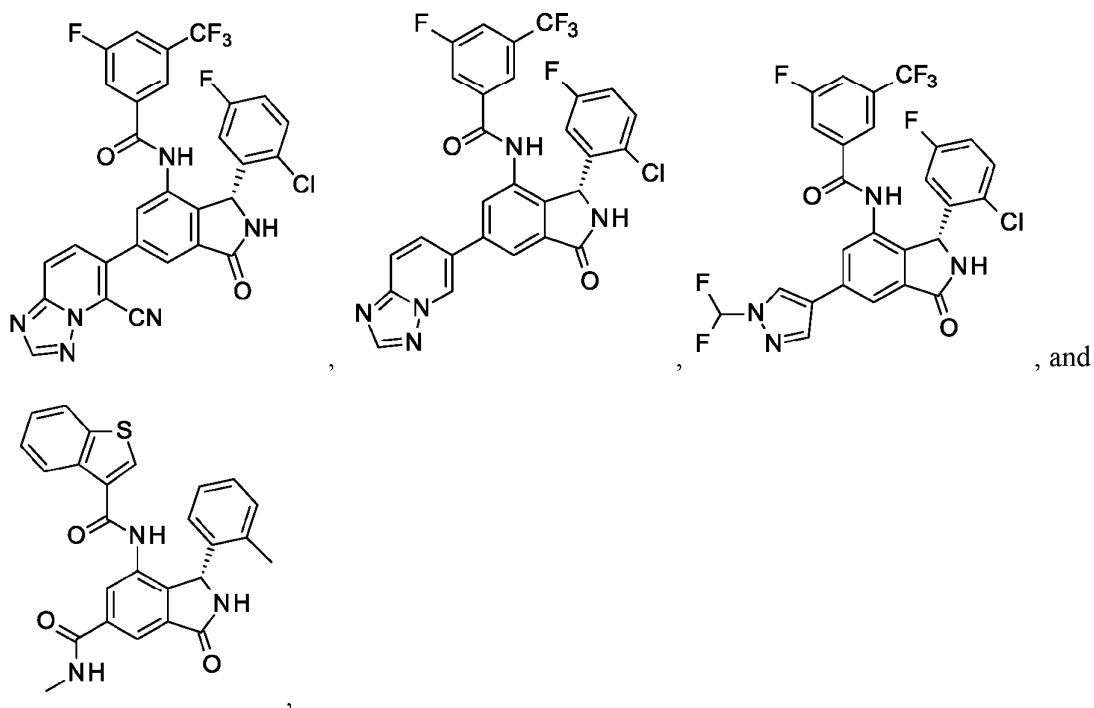
[194] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is



[195] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

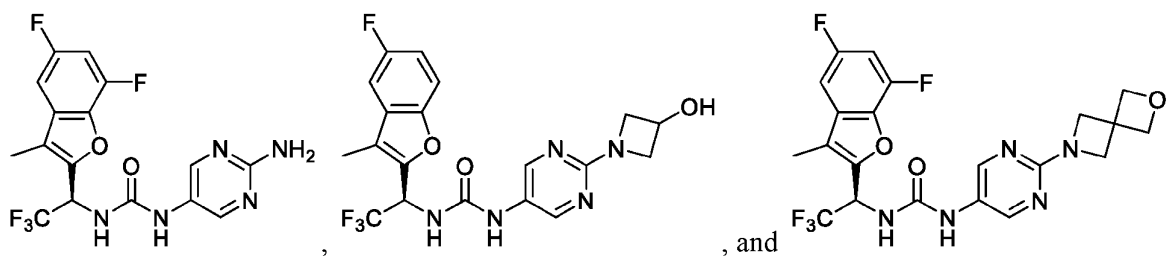
[196] In some aspects of the disclosed methods, the second PI3K α selective inhibitor has a formula selected from:

- 70 -



or a pharmaceutically acceptable salt thereof.

[197] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is disclosed in WO2022/265993 and has a formula selected from:



or a pharmaceutically acceptable salt thereof.

[198] In the disclosed methods, a therapeutically effective amount of the first PI3K α selective inhibitor is administered to the patient in need thereof, and the first PI3K α selective inhibitor functions as an allosteric inhibitor (i.e., the first allosteric inhibitor). In some aspects, the therapeutically effective amount of the first allosteric inhibitor administered to the patient is a 100-1200 mg oral dose BID (i.e.,

administered two times daily). In some aspects, the therapeutically effective amount of the first allosteric inhibitor administered to the patient is 9-75 mg/kg oral dose BID (e.g., 37.5 mg/kg).

[199] In some aspects of the disclosed methods which comprise administering a therapeutically effective amount of a first allosteric inhibitor and a therapeutically effective amount of a second allosteric inhibitor, a synergistic effect may be observed. In some aspects of the disclosed methods, the therapeutically effective amount of the first allosteric inhibitor administered to the patient may be less than a therapeutically effective amount of the first allosteric inhibitor that is required in a method where the second allosteric inhibitor is not administered. In some aspects of the disclosed methods, the therapeutically effective amount of the second allosteric inhibitor that is administered to the patient may be less than a therapeutically effective amount of the second allosteric inhibitor that is required in a method where the first allosteric inhibitor is not administered.

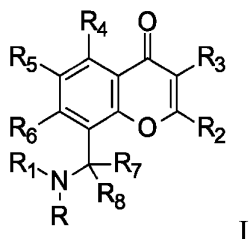
[200] In some aspects of the disclosed methods, the therapeutically effective amount of the first allosteric inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. In some aspects of the disclosed methods, the therapeutically effective amount of the second allosteric inhibitor is effective for reducing PI3K α activity in the patient without inducing adverse events, or while minimizing the risk of adverse events.

[201] In the disclosed methods, the first allosteric inhibitor and the second allosteric inhibitor may be administered sequentially. In some aspects, the methods comprise administering the second allosteric inhibitor after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, the second allosteric inhibitor is administered initially after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, the second allosteric inhibitor is not administered until after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, resistance is characterized by occurrence of a M1043 mutation (e.g., M1043I or M1043L) and/or a C901 mutation (e.g., C901F). In some aspects, a patient has a disease or disorder comprising a M1043I/L mutation and/or a C901F mutation together with a H1047R mutation (optionally wherein the M1043I/L mutation and the C901F mutation are in *cis* on the same allele with the H1047R mutation).

[202] I.C. Use of a Combination of a First Allosteric Inhibitor and a Second Allosteric Inhibitor of Phosphoinositide 3-Kinase (PI3K) for Treating Diseases and Disorders Associated with PI3K Modulation, Where the First Allosteric Inhibitor and the Second Allosteric Inhibitor Bind to the Same Allosteric Pocket

[203] The disclosed methods may relate to methods for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof. The methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3K α selective inhibitor, wherein the first PI3K α selective inhibitor binds the PI3K α allosteric pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047 and (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor binds to the PI3K α allosteric pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. The disclosed methods may comprise administering a PI3K α selective allosteric inhibitor (e.g., the first allosteric inhibitor) and a different PI3K α selective allosteric inhibitor (e.g., the second allosteric inhibitor), where the PI3K α selective allosteric inhibitors bind to the PI3K α allosteric pocket 1. In the disclosed methods, the first allosteric inhibitor and the second allosteric inhibitor are administered simultaneously, separately, or sequentially.

[204] In some aspects of the disclosed methods, the first PI3K α selective inhibitor is an allosteric inhibitor of a Formula I:

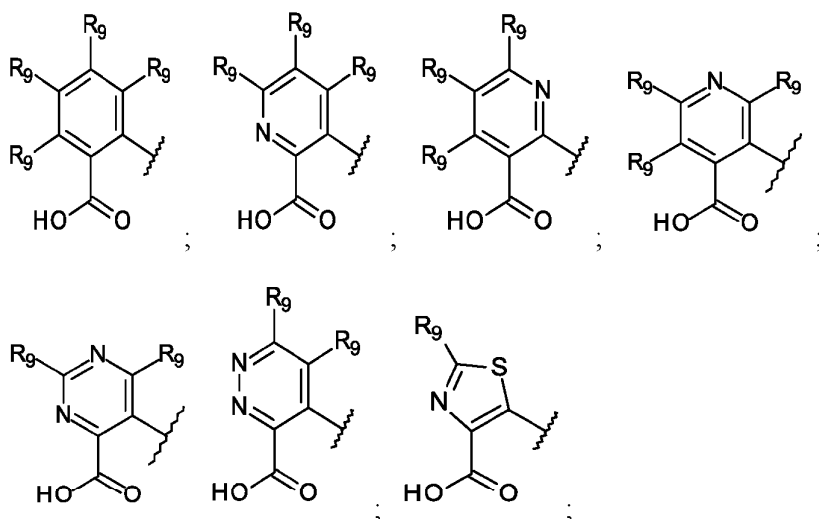


or pharmaceutically acceptable salt thereof, wherein:

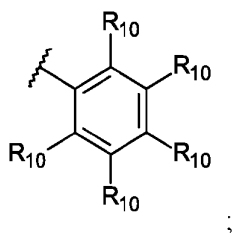
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R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R**₄, **R**₅ and **R**₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

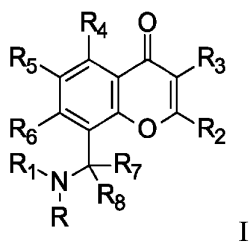
- 74 -

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[205] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor of a Formula I:

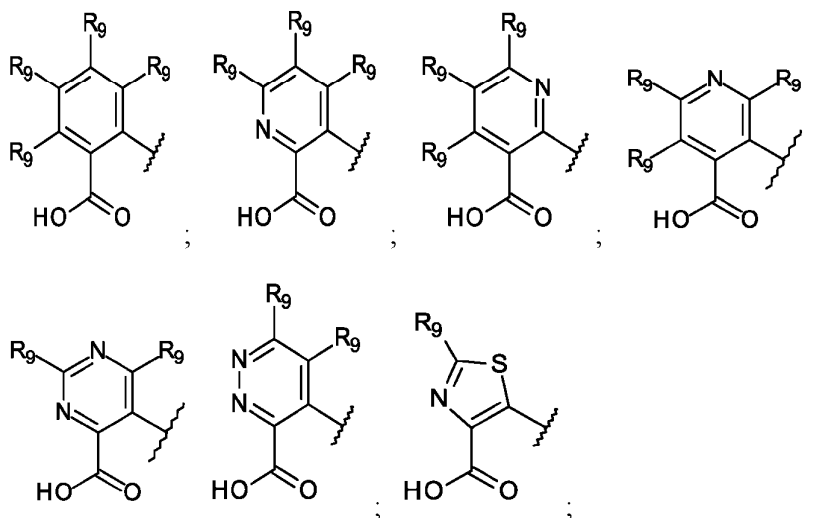


or pharmaceutically acceptable salt thereof, wherein:

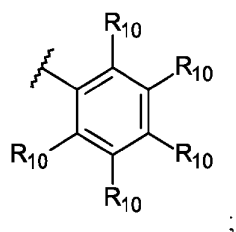
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:

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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅

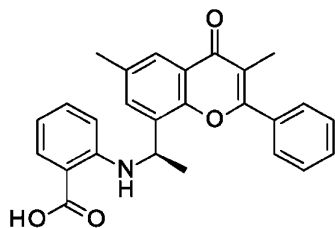
- 76 -

cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[206] In some aspects of the disclosed methods, the first allosteric inhibitor of Formula I and the second allosteric inhibitor of Formula I are different.

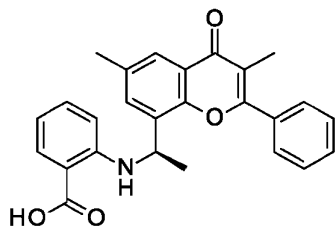
[207] In some aspects of the disclosed methods, the first allosteric inhibitor is of a Formula:



or a pharmaceutically acceptable salt thereof.

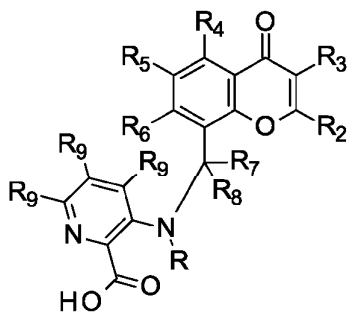
[208] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is not of a formula:

- 77 -



or a pharmaceutically acceptable salt thereof.

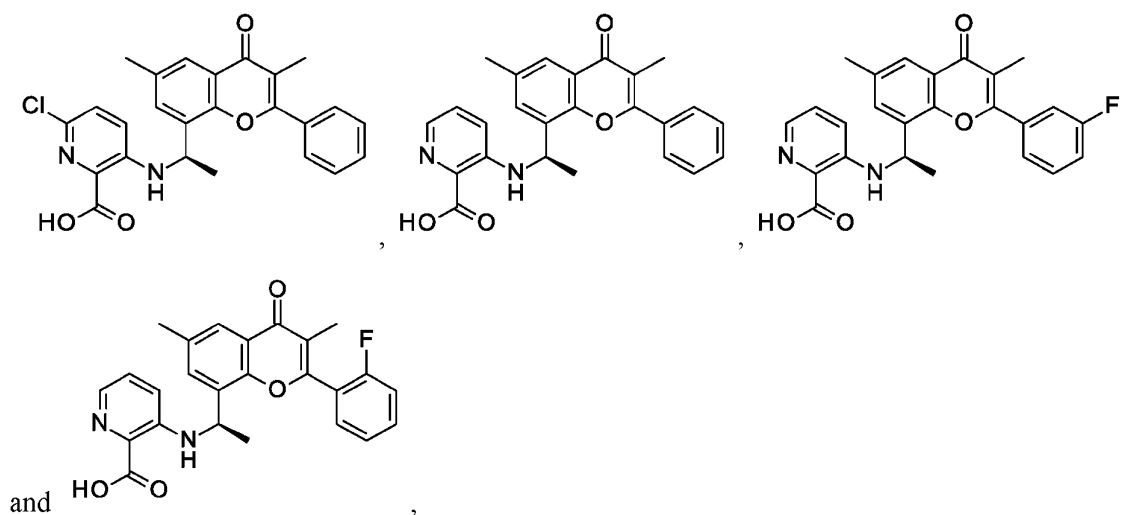
[209] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is an allosteric inhibitor of a formula:



or a pharmaceutically acceptable salt thereof.

[210] In some aspects of the disclosed methods, the second allosteric inhibitor is of a formula selected from:

- 78 -



or a pharmaceutically acceptable salt thereof.

[211] In the disclosed methods, a therapeutically effective amount of the first PI3K α selective inhibitor is administered to the patient in need thereof, and the first PI3K α selective inhibitor functions as an allosteric inhibitor. In some aspects, the therapeutically effective amount of the first allosteric inhibitor administered to the patient is a 100-1200 mg oral dose BID (i.e., administered two times daily). In some aspects, the therapeutically effective amount of the first allosteric inhibitor administered to the patient is 9-75 mg/kg oral dose BID (e.g., 37.5 mg/kg).

[212] In the disclosed methods, a first allosteric inhibitor and a second allosteric inhibitor may be administered sequentially. In some aspects, the methods comprise administering the second allosteric inhibitor after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, the second allosteric inhibitor is administered initially after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, the second allosteric inhibitor is not administered until after the disease or disorder has developed resistance to the first allosteric inhibitor. In some aspects, resistance is characterized by occurrence of a M1043 mutation (e.g., M1043I or M1043L) and/or a C901 mutation (e.g., C901F). In some aspects, a patient may have a disease or disorder comprising a M1043I/L mutation and/or a C901F mutation together with a H1047R mutation (optionally wherein the M1043I/L mutation the C901F mutation

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are in *cis* on the same allele with the H1047R mutation).

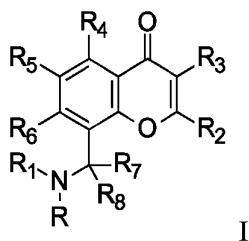
[213] I.D(i). Use of Allosteric Inhibitors for Treating Diseases or Disorders that are Resistant to Treatment with Orthosteric Inhibitors

[214] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a PI3K α selective orthosteric inhibitor. The methods may comprise administering to a patient having the disease or disorder a therapeutically effective amount of a PI3K α selective allosteric inhibitor, wherein the PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047.

[215] In some aspects of the disclosed methods, the patient has a disease or disorder which has developed resistance to treatment with the orthosteric inhibitor after the patient previously was treated with the orthosteric inhibitor. In some aspects of the disclosed methods, the patient has a disease or disorder exhibiting *de novo* resistance to treatment with the orthosteric inhibitor, where the patient was not treated previously with the orthosteric inhibitor.

[216] In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with alpelisib or a pharmaceutically acceptable salt thereof. In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with inavolisib or a pharmaceutically acceptable salt thereof. In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with serabelisib or a pharmaceutically acceptable salt thereof.

[217] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula I:

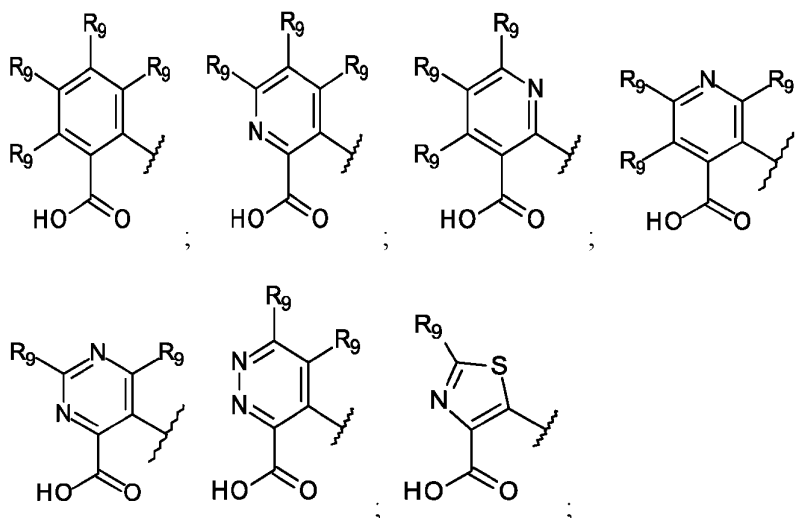


- 80 -

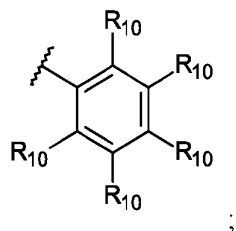
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R**₄, **R**₅ and **R**₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

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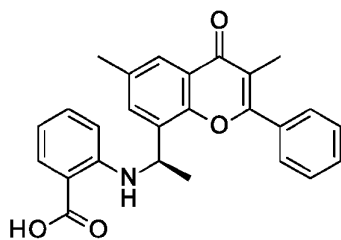
R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

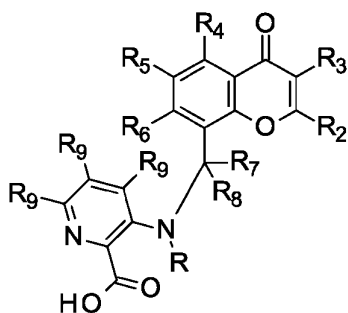
[218] In some aspects of the disclosed methods, the allosteric inhibitor is not of a formula:



or a pharmaceutically acceptable salt thereof.

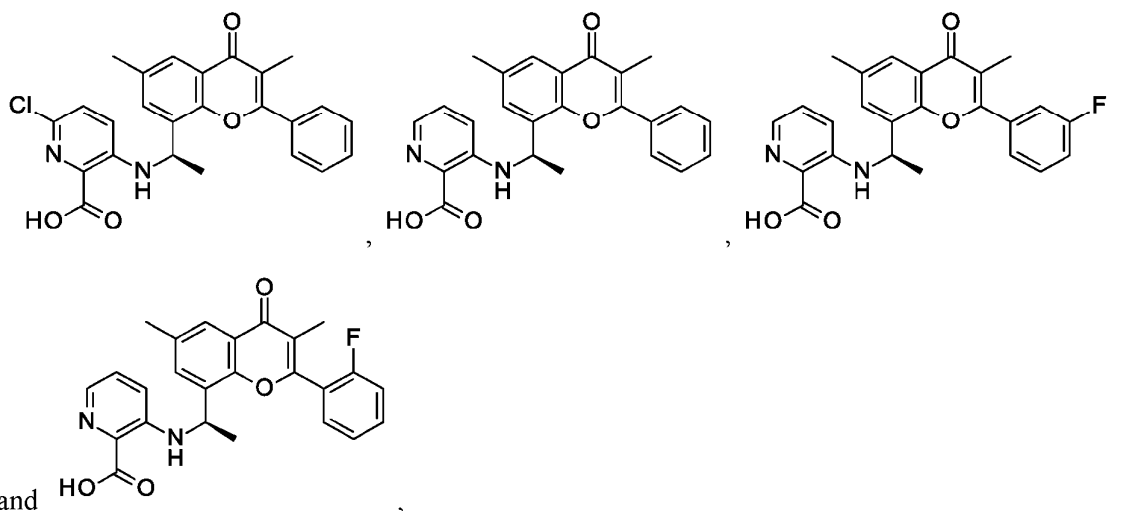
[219] In some aspects of the disclosed methods, the allosteric inhibitor is of a formula:

- 82 -



or a pharmaceutically acceptable salt thereof.

[220] In some aspects of the disclosed methods, the allosteric inhibitor is of a formula selected from:



or a pharmaceutically acceptable salt thereof.

[221] The disclosed methods may include administered a therapeutically effective amount of a PI3K α selective allosteric inhibitor to a patient having a disease or disorder that is resistant to treatment with an orthosteric inhibitor. In some aspects, the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

[222] I.D(ii). Use of Other Allosteric Inhibitors for Treating Diseases or Disorders that have Resistance to Orthosteric Inhibitors

[223] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a PI3K α selective orthosteric inhibitor. The methods may comprise administering to a patient having the disease or disorder a therapeutically effective amount of a PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2 and optionally may form one or more interactions with one or more amino acids selected from L911, F937, F1002, E1012, and D1018.

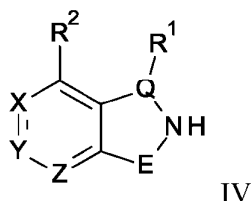
[224] In some aspects of the disclosed methods, the patient has developed a disease or disorder that is resistant to treatment with the orthosteric inhibitor after the patient previously was treated with the orthosteric inhibitor. In some aspects of the disclosed methods, the patient has a disease or disorder exhibiting *de novo* resistance to treatment with the orthosteric inhibitor, where the patient was not treated previously with the orthosteric inhibitor.

[225] In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with alpelisib or a pharmaceutically acceptable salt thereof. In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with inavolisib or a pharmaceutically acceptable salt thereof. In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with serabelisib or a pharmaceutically acceptable salt thereof.

[226] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor is an allosteric inhibitor disclosed in WO2021/222556, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/288242, WO2023/081757, or WO2023/081759, the contents of which are incorporated herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein.

[227] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula IV:

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or a pharmaceutically acceptable salt thereof, wherein:

E is $-\text{C}(\text{O})-$, $-\text{C}(\text{R}^{\text{E}})_2-$, $-\text{C}(\text{R}^{\text{E}})_2\text{C}(\text{R}^{\text{E}})_2-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{\text{E}})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{E}})-$, or $-\text{C}(\text{R}^{\text{E}})_2\text{C}(\text{O})-$;

Q is CH, $\text{C}(\text{R}^{\text{Q}})$, or N;

X is CH, $\text{C}(\text{R}^{\text{X}})$, or N;

Y is CH, $\text{C}(\text{R}^{\text{Y}})$, or N;

Z is CH, $\text{C}(\text{R}^{\text{Z}})$, or N;

R^1 is $-\text{L}^1-\text{R}^{1\text{A}}$;

R^2 is $-\text{L}^2-\text{R}^{2\text{A}}$;

each instance of R^{E} is independently H or $-\text{L}^{\text{E}}-\text{R}^{\text{EA}}$;

R^{Q} is $-\text{L}^{\text{Q}}-\text{R}^{\text{QA}}$;

R^{X} is $-\text{L}^{\text{X}}-\text{R}^{\text{XA}}$;

R^{Y} is $-\text{L}^{\text{Y}}-\text{R}^{\text{YA}}$;

R^{Z} is $-\text{L}^{\text{Z}}-\text{R}^{\text{ZA}}$, or

two instances of R^{E} are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC} ;

[228] R^{Q} and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is

substituted with p instances of R^{Q1C} ;

[229] R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC} ; each of L^1 , L^2 , L^E , L^Q , L^X , L^Y , and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, $-N(R)-$, $-N(R)C(O)-$, $-N(R)C(NR)-$, $-N(R)C(NOR)-$, $-N(R)C(NCN)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

[230] R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C} ;

[231] R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

[232] R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

[233] R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

[234] R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

[235] R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

[236] R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

[237] R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

[238] each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$;

[239] each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

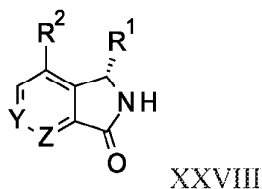
[240] each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

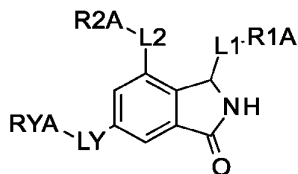
[241] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula XXVIII:

- 87 -



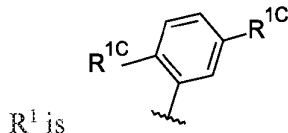
or a pharmaceutically acceptable salt thereof.

[242] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula:



or a pharmaceutically acceptable salt thereof.

[243] In some aspects, the allosteric inhibitor is of a Formula in which



[244] In some aspects, the allosteric inhibitor is of a Formula in which each instance of R^{1C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[245] In some aspects, the allosteric inhibitor is of a Formula in which each instance of R^{1C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[246] In some aspects, the allosteric inhibitor is of a Formula in which R² is -N(H)C(O)-R^{2A}, -N(H)C(O)N(H)-R^{2A}, -C(O)N(H)-R^{2A}, -N(H)-R^{2A}, -S(O)₂CH₂-R^{2A}, -CH₂S(O)₂-R^{2A}, or -C(H)(CH₃)OH.

[247] In some aspects, the allosteric inhibitor is of a Formula in which R^{2A} is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

[248] In some aspects, the allosteric inhibitor is of a Formula in which each instance of R^{2C} is

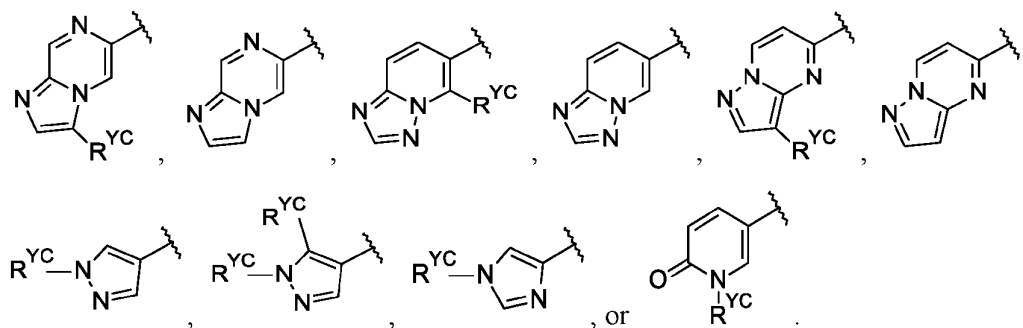
- 88 -

independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[249] In some aspects, the allosteric inhibitor is of a Formula in which each instance of R^{2C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[250] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r⁶ instances of R^{YC}.

In some aspects, the allosteric inhibitor is of a Formula in which R^{YA} is

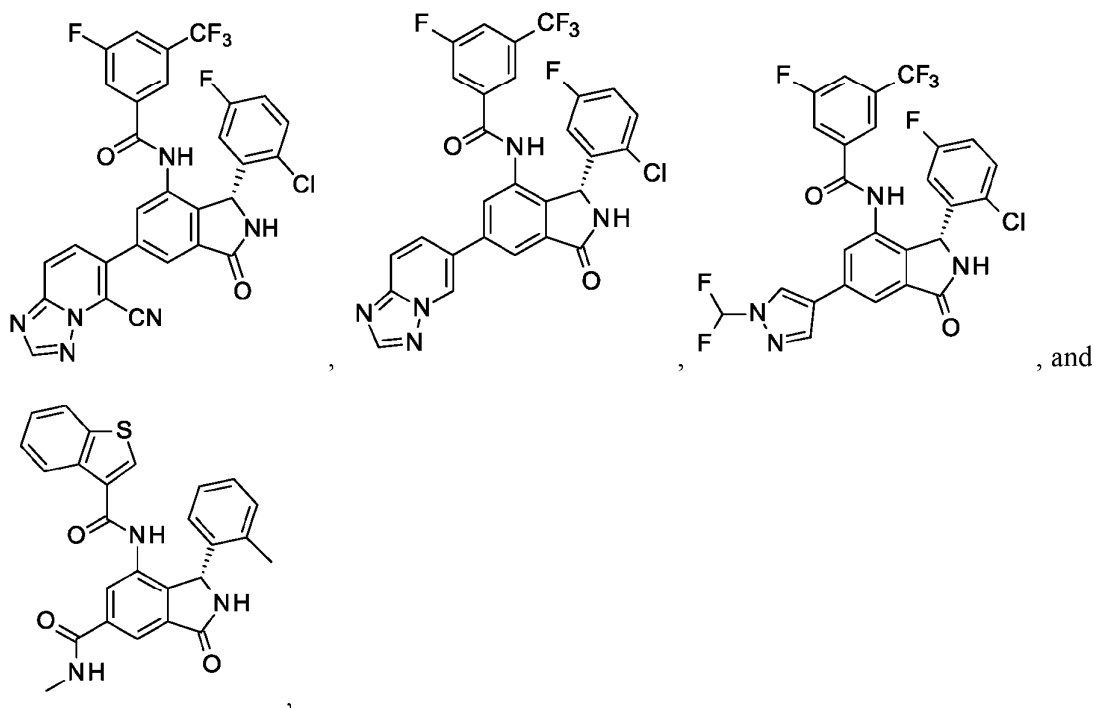


[251] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

[252] In some aspects of the disclosed methods, the allosteric inhibitor has a formula selected from:

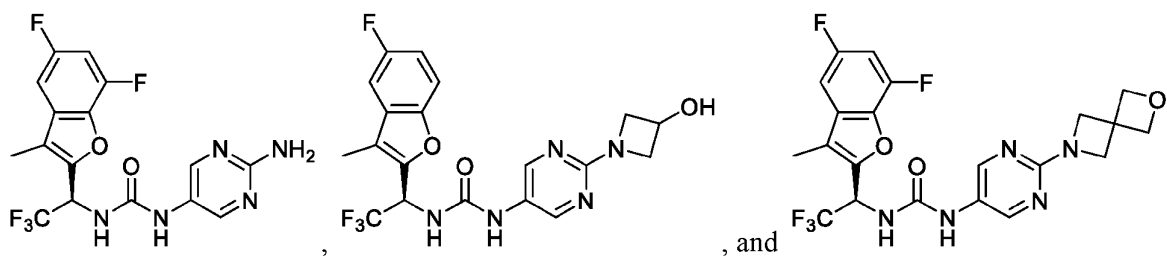
[253] In some aspects of the disclosed methods, the second PI3K α selective inhibitor has a formula selected from:

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or a pharmaceutically acceptable salt thereof.

[254] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is disclosed in WO2022/265993 and has a formula selected from:



or a pharmaceutically acceptable salt thereof.

[255] The disclosed methods may include administered a therapeutically effective amount of a PI3K α selective allosteric inhibitor to a patient having a disease or disorder that is resistant to treatment with an orthosteric inhibitor. In some aspects, the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor

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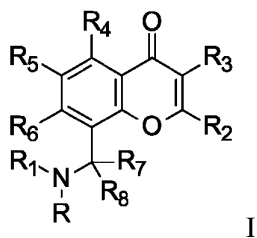
degrader (SERD).

[256] LD (iii) Use of Allosteric Inhibitors for Treating Diseases or Disorders that have Resistance to Another Allosteric Inhibitor

[257] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a first PI3K α selective allosteric inhibitor, wherein the first PI3K α selective allosteric inhibitor binds to the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. The methods may comprise administering to a patient having the disease or disorder a therapeutically effective amount of a second different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 1 and optionally form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047.

[258] In some aspects of the disclosed methods, the patient has a disease or disorder which has developed resistance to treatment with the first allosteric inhibitor after the patient previously was treated with the first allosteric inhibitor. In some aspects of the disclosed methods, the patient has a disease or disorder exhibiting *de novo* resistance to treatment with the first allosteric inhibitor, where the patient was not treated previously with the first allosteric inhibitor.

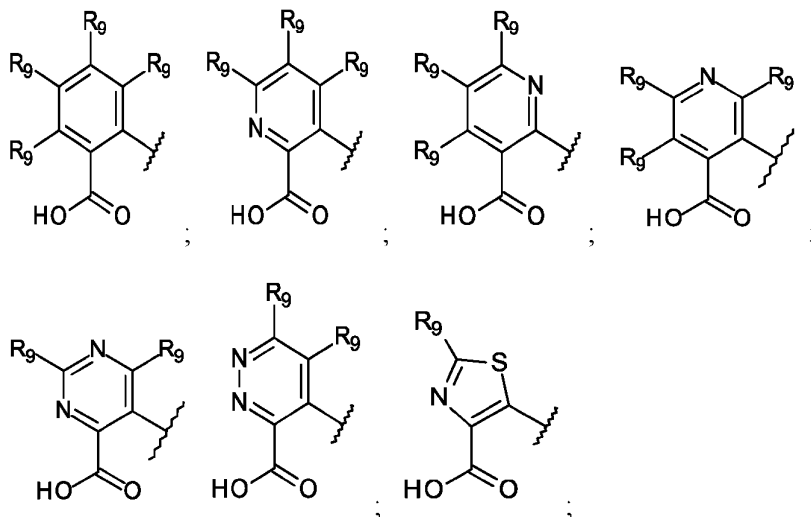
[259] In some aspects of the disclosed methods, the patient is resistant to treatment with a first allosteric inhibitor of a Formula I:



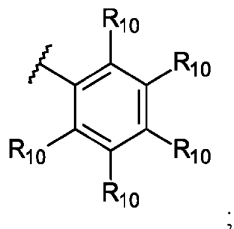
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

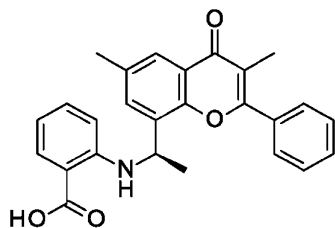
R₈ is -H or C₁-C₆ alkyl;

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each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

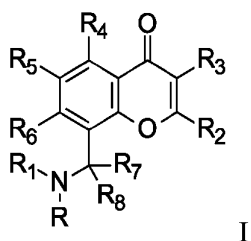
[260] In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with an allosteric inhibitor of a formula:



or a pharmaceutically acceptable salt thereof.

[261] In some aspects of the disclosed methods, the patient that is resistant to treatment with the first allosteric inhibitor is administered a therapeutically effective amount of a second allosteric inhibitor of a Formula I:

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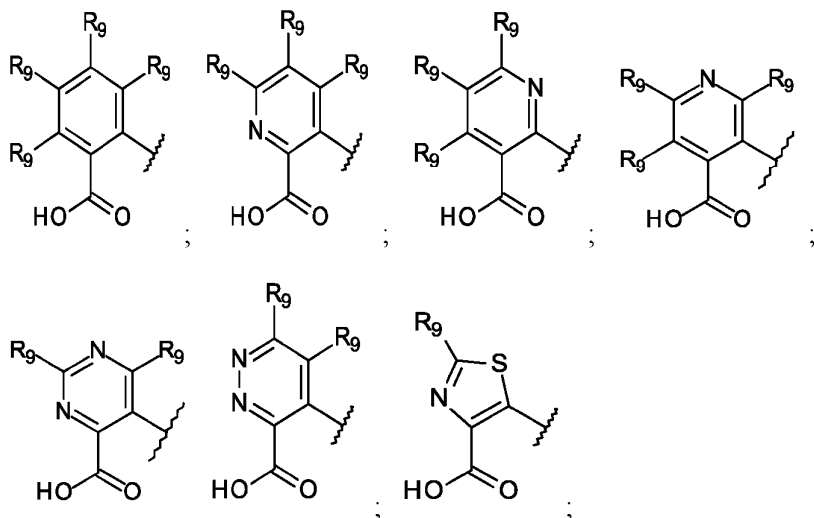


I

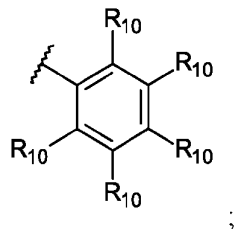
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from

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N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

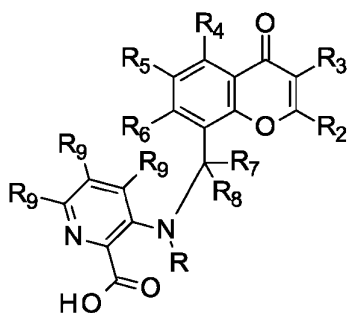
R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

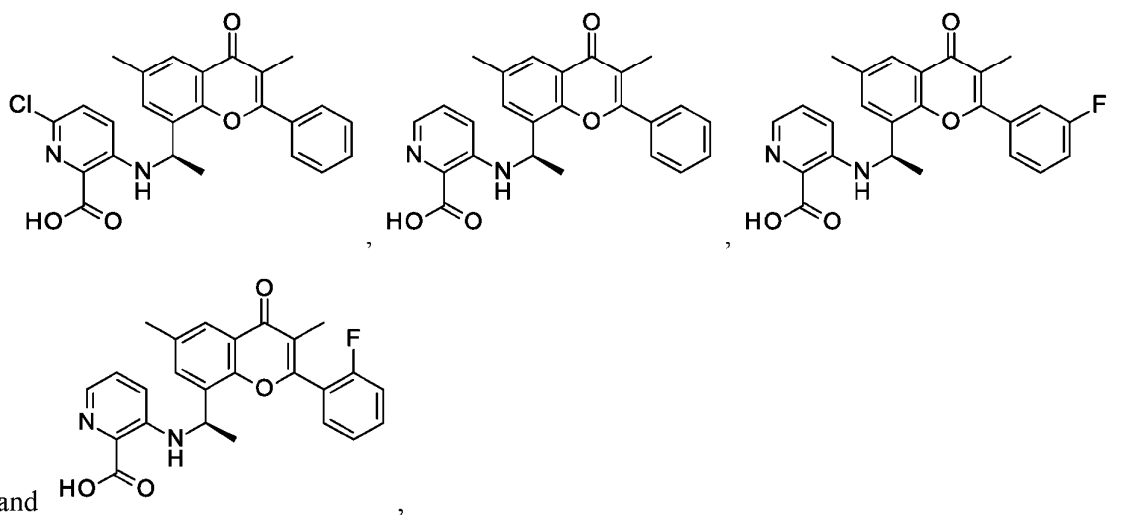
[262] In some aspects of the disclosed methods, the allosteric inhibitor administered to the patient is of a formula:

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or a pharmaceutically acceptable salt thereof.

[263] In some aspects of the disclosed methods, the allosteric inhibitor administered to the patient is of a formula selected from:



or a pharmaceutically acceptable salt thereof.

[264] The disclosed methods may include administered a therapeutically effective amount of a PI3K α selective allosteric inhibitor to a patient having a disease or disorder that is resistant to treatment with a different PI3K α selective allosteric inhibitor. In some aspects, the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

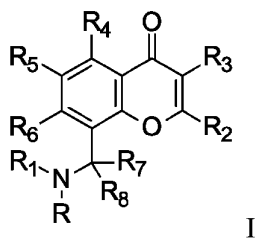
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[265] LD.(iv) Use of Allosteric Inhibitors for Treating Diseases or Disorders that have Acquired Resistance to Another Allosteric Inhibitor

[266] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α that is resistant to treatment with a first PI3K α selective allosteric inhibitor, wherein the first PI3K α selective allosteric inhibitor binds the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. The methods may comprise administering to a patient having the disease or disorder a therapeutically effective amount of a second different PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2 and optionally may form an interaction with one or more amino acids selected from L911, F937, F1002, E1012, and D1018.

[267] In some aspects of the disclosed methods, the patient has a disease or disorder which has developed resistance to treatment with the first allosteric inhibitor after the patient previously was treated with the first allosteric inhibitor. In some aspects of the disclosed methods, the patient has a disease or disorder exhibiting *de novo* resistance to treatment with the first allosteric inhibitor, where the patient was not treated previously with the first allosteric inhibitor.

[268] In some aspects of the disclosed methods, the patient is resistant to treatment with a first allosteric inhibitor of a Formula I:

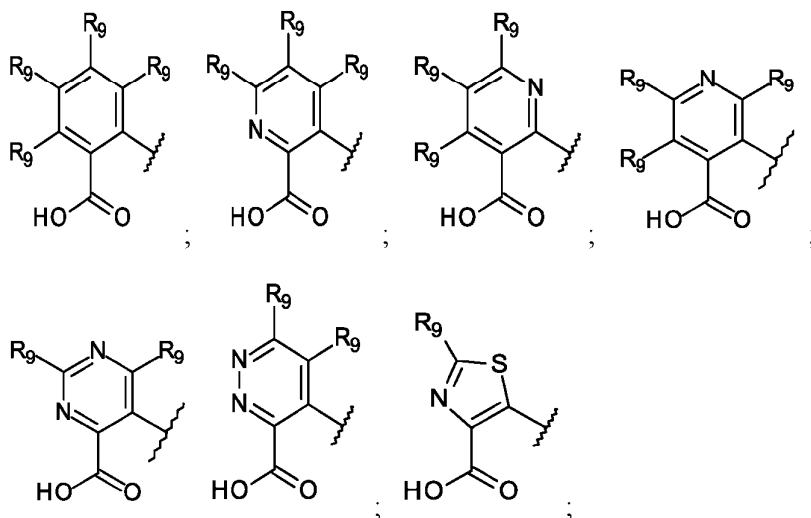


or pharmaceutically acceptable salt thereof, wherein:

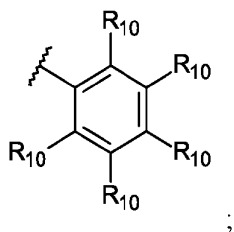
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:

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R_2 is a group of the formula:



R_3 is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of R_4 , R_5 and R_6 is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R_7 is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R_8 is -H or C₁-C₆ alkyl;

each R_9 is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅

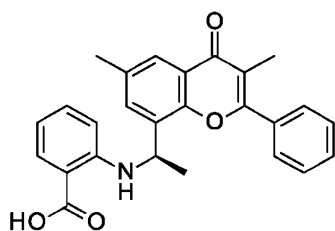
- 98 -

cycloalkyl;

each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

[269] each **R**₁₁ is independently -H or C₁-C₃ alkyl.

[270] In some aspects of the disclosed methods, the disease or disorder is resistant to treatment with an allosteric inhibitor of a formula:

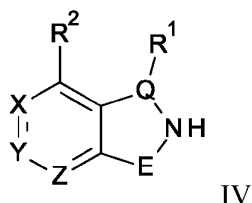


or a pharmaceutically acceptable salt thereof.

[271] In some aspects of the disclosed methods, the patient that is resistant to treatment with the first allosteric inhibitor is administered a therapeutically effective amount of a second allosteric inhibitor as disclosed in WO2021/222556, WO2022/265993, WO2023/018636, WO2023/039532, WO2023/288242, WO2023/081757, or WO2023/081759, the contents of which are incorporated

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herein by reference in their entireties with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein. In some aspects of the disclosed methods, the second allosteric inhibitor is of a Formula IV:



or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)₂-, -C(R^E)₂C(R^E)₂-, -C(S)-, -S(O)₂-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)₂C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R¹ is -L¹-R^{1A};

R² is -L²-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

[272] R^Q and R¹ are taken together with their intervening atoms to form a 4-8 membered saturated or

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partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C} ;

[273] R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC} ; each of L^1 , L^2 , L^E , L^Q , L^X , L^Y , and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, $-N(R)-$, $-N(R)C(O)-$, $-N(R)C(NR)-$, $-N(R)C(NOR)-$, $-N(R)C(NCN)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

[274] R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C} ;

[275] R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

[276] R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

[277] R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

[278] R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

[279] R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

[280] R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

[281] R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

[282] each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$;

[283] each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or

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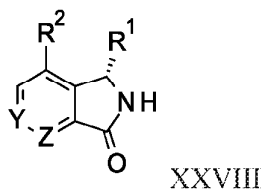
partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

[284] each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

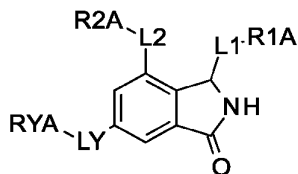
[285] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula XXVIII:

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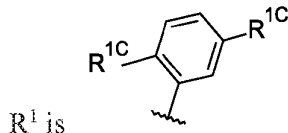
or a pharmaceutically acceptable salt thereof.

[286] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula:



or a pharmaceutically acceptable salt thereof.

[287] In some aspects, the allosteric inhibitor is of a formula in which



[288] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[289] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[290] In some aspects, the allosteric inhibitor is of a formula in which R² is -N(H)C(O)-R^{2A}, -N(H)C(O)N(H)-R^{2A}, -C(O)N(H)-R^{2A}, -N(H)-R^{2A}, -S(O)₂CH₂-R^{2A}, -CH₂S(O)₂-R^{2A}, or -C(H)(CH₃)OH.

[291] In some aspects, the allosteric inhibitor is of a formula in which R^{2A} is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

[292] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is

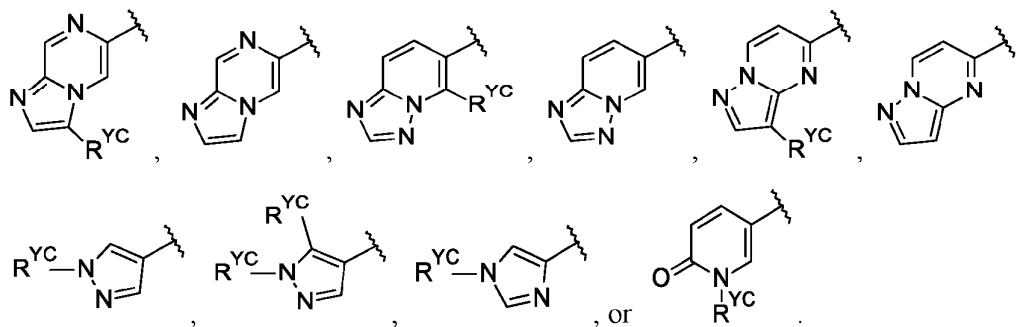
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independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[293] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[294] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r⁶ instances of R^{YC}.

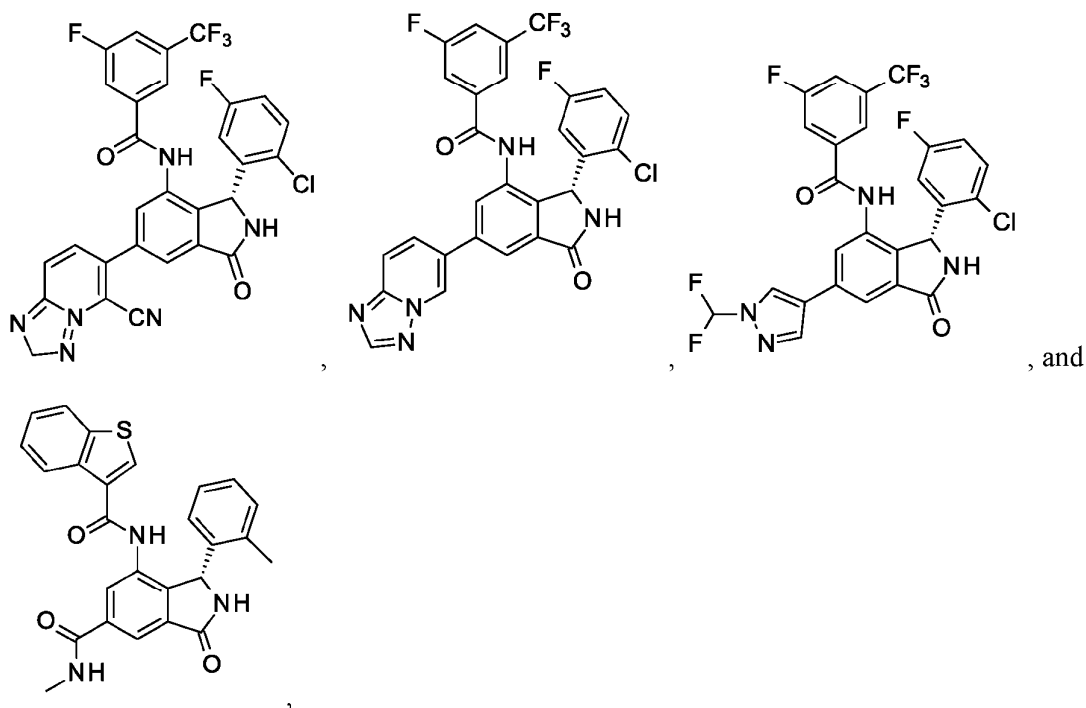
[295] In some aspects, the allosteric inhibitor is of a formula in which R^{YA} is



[296] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

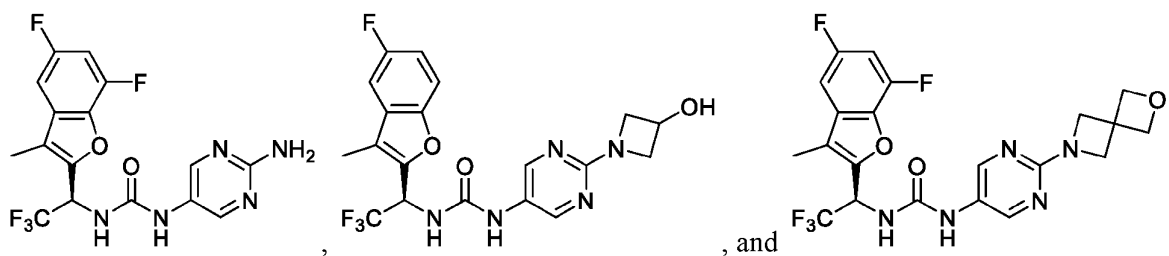
[297] In some aspects of the disclosed methods, the allosteric inhibitor administered to the patient has a formula selected from:

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or a pharmaceutically acceptable salt thereof.

[298] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is disclosed in WO2022/265993 and has a formula selected from:



or a pharmaceutically acceptable salt thereof.

[299] The disclosed methods may include administered a therapeutically effective amount of a PI3K α selective allosteric inhibitor to a patient having a disease or disorder that is resistant to treatment with another PI3K α selective allosteric inhibitor. In some aspects, the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective

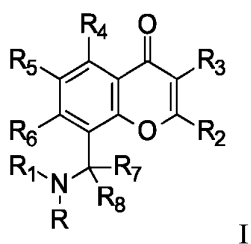
- 105 -

estrogen receptor degrader (SERD).

[300] I.E. Orthosteric Inhibitors for Treating M1043I/L + H1047R Cancer

[301] In some aspects, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient has cancer comprising a M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), optionally after the patient was treated previously with a therapeutically effective amount a PI3K α selective allosteric inhibitor. In the disclosed methods, the PI3K α selective allosteric inhibitor may bind to the PI3K α allosteric pocket 1 and optionally may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. In the disclosed methods, the patient may have a cancer exhibiting acquired resistance to treatment with the PI3K α selective allosteric inhibitor or the patient may have a cancer exhibiting de novo resistance to treatment with the PI3K α selective allosteric inhibitor; and in the disclosed methods, the patient may be administered a therapeutically effective amount of a PI3K α selective orthosteric inhibitor.

[302] In some aspects of the disclosed methods, the patient was previously treated with a PI3K α selective allosteric inhibitor of a Formula I:

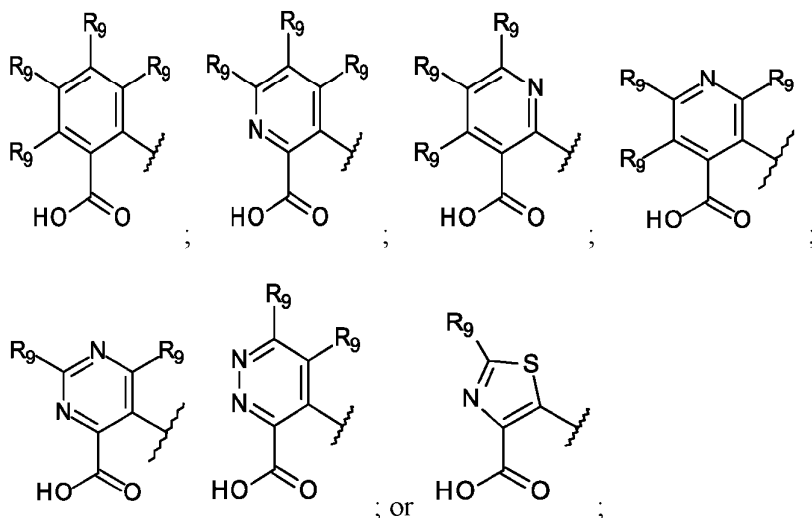


or pharmaceutically acceptable salt thereof, wherein:

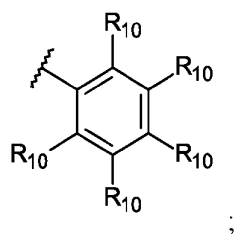
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:

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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

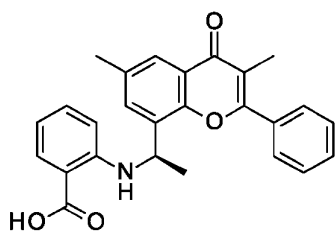
each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅

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cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[303] In some aspects of the disclosed methods, the patient was treated previously with a therapeutically effective amount of a PI3K α selective allosteric inhibitor of a formula:



or a pharmaceutically acceptable salt thereof.

[304] In some aspects of the disclosed methods, the therapeutically effective amount of the PI3K α selective allosteric inhibitor that was administered to the patient was a 100-1200 mg oral dose administered two times daily. In some aspects of the disclosed methods, the therapeutically effective amount of the first PI3K α selective inhibitor that was administered to the patient was a 9-75 mg/kg oral dose administered two times daily (e.g., 37.5 mg/kg oral dose administered two times daily). In

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the disclosed methods, the patient may have acquired resistance to treatment with the PI3K α selective allosteric inhibitor which was administered at the indicated dose.

[305] In the disclosed methods, a therapeutically effective amount of the PI3K α selective orthosteric inhibitor is administered to the patient in need thereof. In some aspects, the therapeutically effective amount of the PI3K α selective orthosteric inhibitor administered to the patient is a 300 mg oral dose QD (i.e., administered once a day) or less than about a 300 mg oral dose QD, such as less than about 250, 200, 150, 100, or 50 mg oral dose QD.

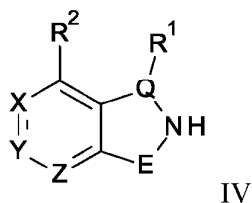
[306] In some aspects, the disclosed methods comprise administering a patient a therapeutically effective amount of a PI3K α selective orthosteric inhibitor and the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD). In some embodiments, the administered PI3K α selective orthosteric inhibitor is selected from alpelisib, inavolisib, serabelisib, or pharmaceutically acceptable salts thereof.

[307] 1.F(i). Allosteric Inhibitors for Treating M1043I/L + H1047R Cancer

[308] In some aspects, the disclosed methods relate to method for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient has a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in cis) with an H1047R mutation and/or a C901 mutation (e.g., C901F optionally in cis) with an H1047R mutation. The methods comprise administering to the patient a therapeutically effective amount of a PI3K α selective allosteric inhibitor that binds to the PI3K α allosteric pocket 2 and optionally may form an interaction with one or more amino acids selected from L911, F937, F1002, E1012, and D1018.

[309] In some aspects, the PI3K α selective allosteric inhibitor that is administered to the patient is of a Formula IV:

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or a pharmaceutically acceptable salt thereof, wherein:

E is $-\text{C}(\text{O})-$, $-\text{C}(\text{R}^{\text{E}})_2-$, $-\text{C}(\text{R}^{\text{E}})_2\text{C}(\text{R}^{\text{E}})_2-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{\text{E}})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{E}})-$, or $-\text{C}(\text{R}^{\text{E}})_2\text{C}(\text{O})-$;

Q is CH, $\text{C}(\text{R}^{\text{Q}})$, or N;

X is CH, $\text{C}(\text{R}^{\text{X}})$, or N;

Y is CH, $\text{C}(\text{R}^{\text{Y}})$, or N;

Z is CH, $\text{C}(\text{R}^{\text{Z}})$, or N;

R^1 is $-\text{L}^1-\text{R}^{1\text{A}}$;

R^2 is $-\text{L}^2-\text{R}^{2\text{A}}$;

each instance of R^{E} is independently H or $-\text{L}^{\text{E}}-\text{R}^{\text{EA}}$;

R^{Q} is $-\text{L}^{\text{Q}}-\text{R}^{\text{QA}}$;

R^{X} is $-\text{L}^{\text{X}}-\text{R}^{\text{XA}}$;

R^{Y} is $-\text{L}^{\text{Y}}-\text{R}^{\text{YA}}$;

R^{Z} is $-\text{L}^{\text{Z}}-\text{R}^{\text{ZA}}$, or

two instances of R^{E} are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC} ;

R^{Q} and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is

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substituted with p instances of R^{Q1C} ;

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC} ; each of L^1 , L^2 , L^E , L^Q , L^X , L^Y , and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, $-N(R)-$, $-N(R)C(O)-$, $-N(R)C(NR)-$, $-N(R)C(NOR)-$, $-N(R)C(NCN)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C} ;

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$; each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12

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membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

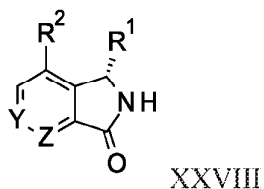
each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

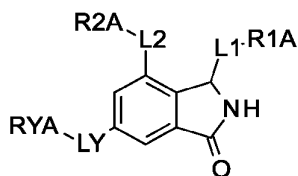
[310] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula XXVIII:

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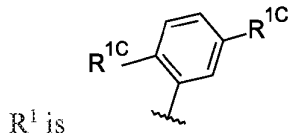
or a pharmaceutically acceptable salt thereof.

[311] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula:



or a pharmaceutically acceptable salt thereof.

[312] In some aspects, the allosteric inhibitor is of a formula in which



[313] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[314] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[315] In some aspects, the allosteric inhibitor is of a formula in which R² is -N(H)C(O)-R^{2A}, -N(H)C(O)N(H)-R^{2A}, -C(O)N(H)-R^{2A}, -N(H)-R^{2A}, -S(O)₂CH₂-R^{2A}, -CH₂S(O)₂-R^{2A}, or -C(H)(CH₃)OH.

[316] In some aspects, the allosteric inhibitor is of a formula in which R^{2A} is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

[317] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is

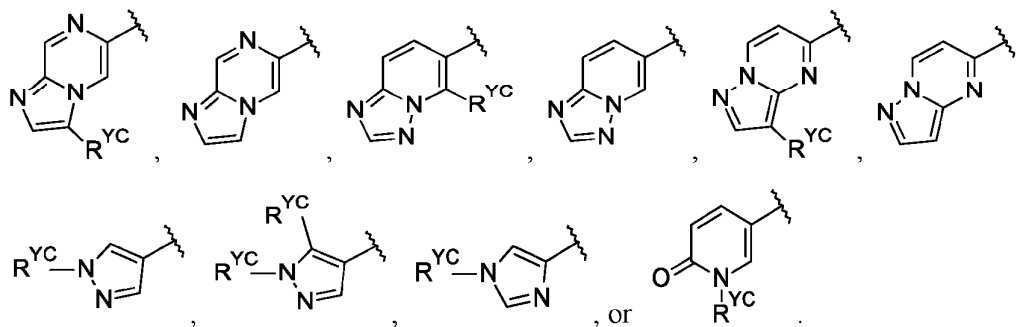
- 113 -

independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[318] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[319] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r⁶ instances of R^{YC}.

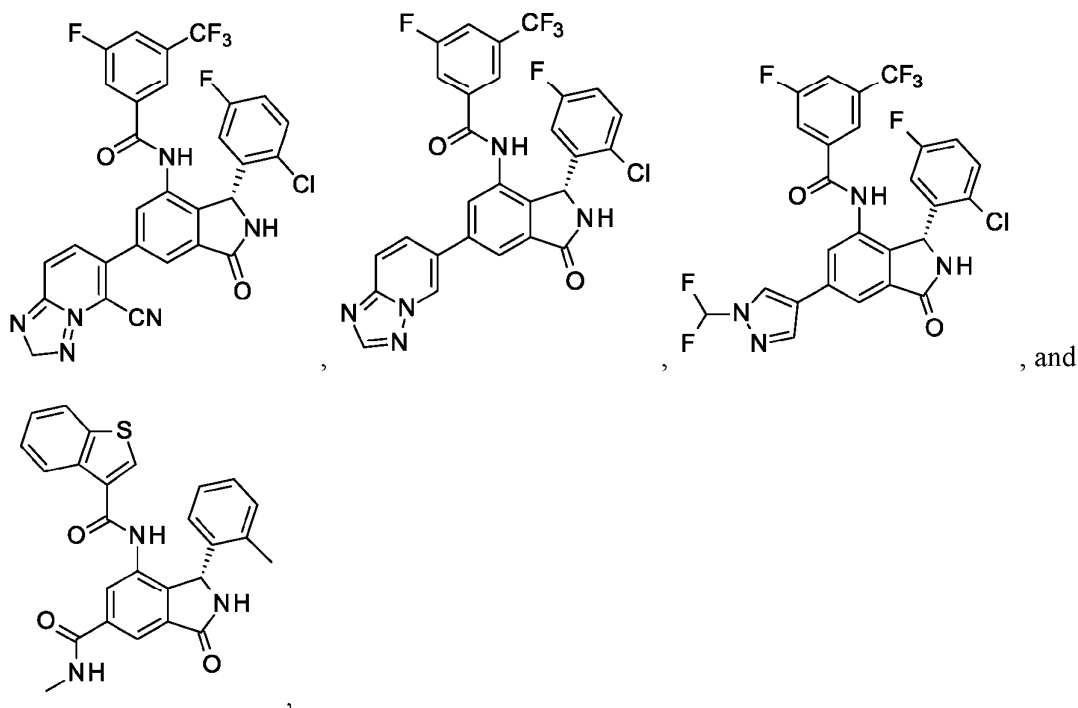
[320] In some aspects, the allosteric inhibitor is of a formula in which R^{YA} is



[321] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

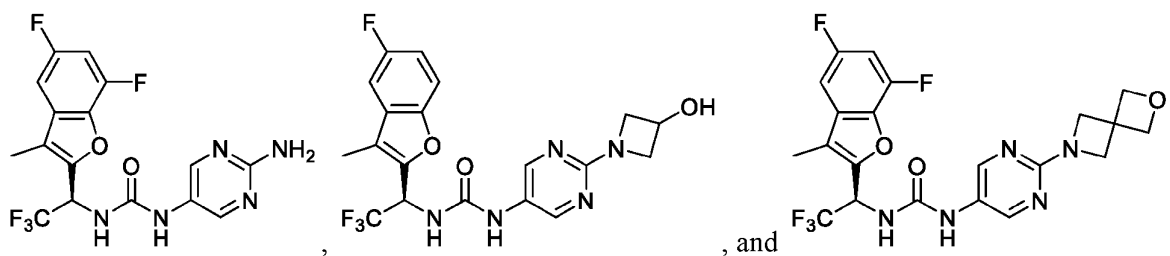
[322] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is administered to the patient is of a formula selected from:

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or a pharmaceutically acceptable salt thereof.

[323] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is disclosed in WO2022/265993 and has a formula selected from:



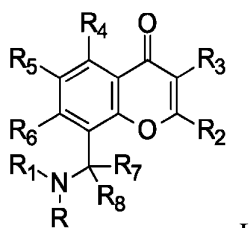
or a pharmaceutically acceptable salt thereof

[324] In some aspects of the disclosed methods, the patient has a cancer which has acquired the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), after the patient was treated previously with a therapeutically effective amount of a first PI3K α selective allosteric inhibitor that

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binds to the PI3K α pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. In some aspects of the disclosed methods, the patient has a cancer comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047 R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation) without the patient having been treated previously with a therapeutically effective amount of a first PI3K α selective allosteric inhibitor that binds to the PI3K α pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047.

[325] In some aspects of the disclosed methods, the patient has a cancer which has acquired the M1043I/L mutation (optionally in *cis* with the H1047R mutation) after the patient was treated previously with a therapeutically effective amount of a first PI3K α selective allosteric inhibitor of a Formula I

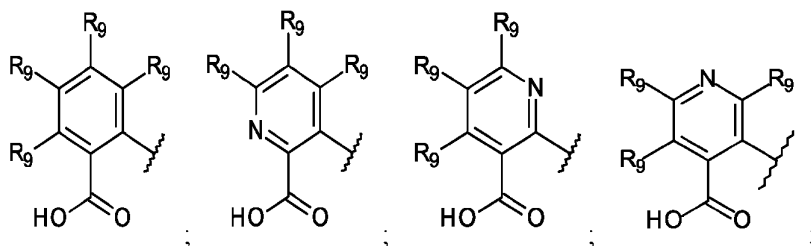


I

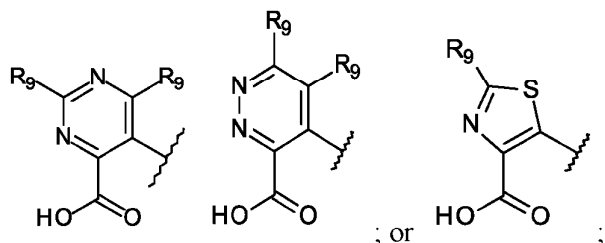
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

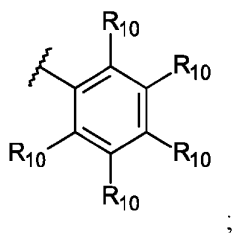
R₁ is a group of the formula:



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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

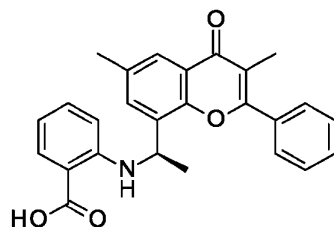
each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle

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selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each R₁₁ is independently -H or C₁-C₃ alkyl.

[326] In some aspects of the disclosed methods, the therapeutically effective amount of the PI3K α selective allosteric inhibitor of Formula I that was administered to the patient was a 100-1200 mg oral dose administered two times daily. In some aspects of the disclosed methods, the therapeutically effective amount of the PI3K α selective allosteric inhibitor of Formula I that was administered to the patient was a 9-75 mg/kg oral dose administered two times daily (e.g., 37.5 mg/kg oral dose administered two times daily). In the disclosed methods, the patient may have a cancer which acquired resistance after the patient was administered the PI3K α selective allosteric inhibitor at the indicated dose.

[327] In some aspects of the disclosed methods, the patient was treated previously with a therapeutically effective amount of a PI3K α selective inhibitor of a formula:



or a pharmaceutically acceptable salt thereof.

[328] In the disclosed methods, the patient may have a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g, C901F

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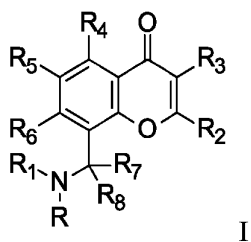
optionally in *cis* with an H1047R mutation), and the patient further may have a cancer comprising one or more mutations selected from E542K, E545K, E453Q/K, and E726K. In some aspects, the patient in need thereof may have advanced, or metastatic breast cancer that is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[329] In some aspects, the disclosed methods comprise administering to the patient a therapeutically effective amount of a PI3K α selective allosteric inhibitor and the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

[330] 1.F(ii). Other Allosteric Inhibitors for Treating M1043I/L + H1047R Cancer

[331] In some aspects, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, wherein the patient has a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation). The methods comprise administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor that binds to the PI3K α pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047.

[332] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is administered to the patient is of a Formula I:

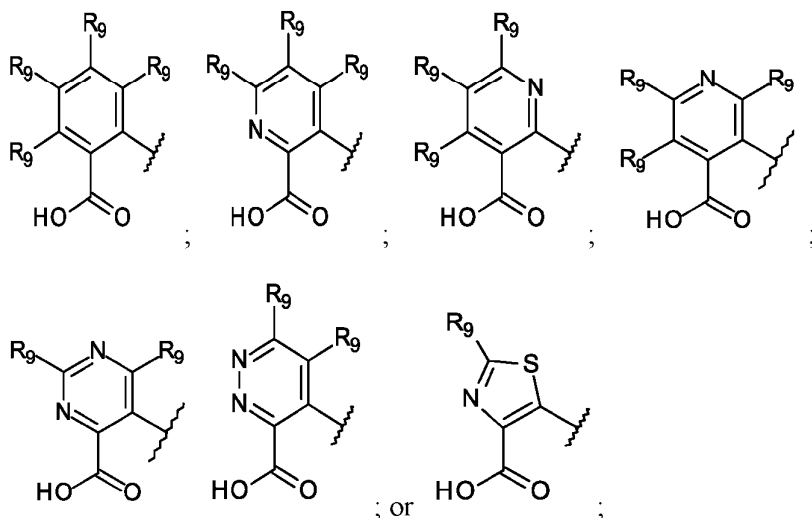


or pharmaceutically acceptable salt thereof, wherein:

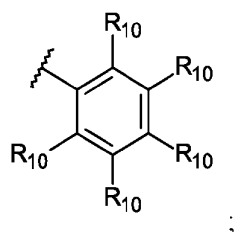
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:

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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

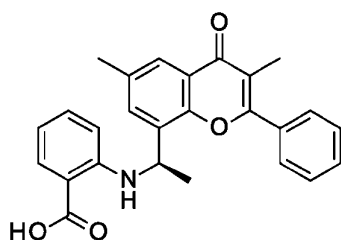
each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅

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cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

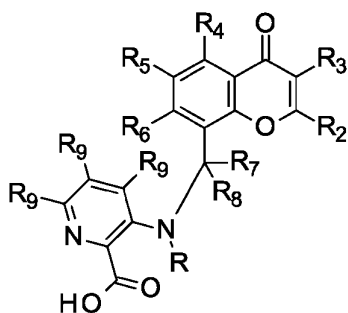
[333] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is administered to the patient is not of a formula:



or a pharmaceutically acceptable salt thereof.

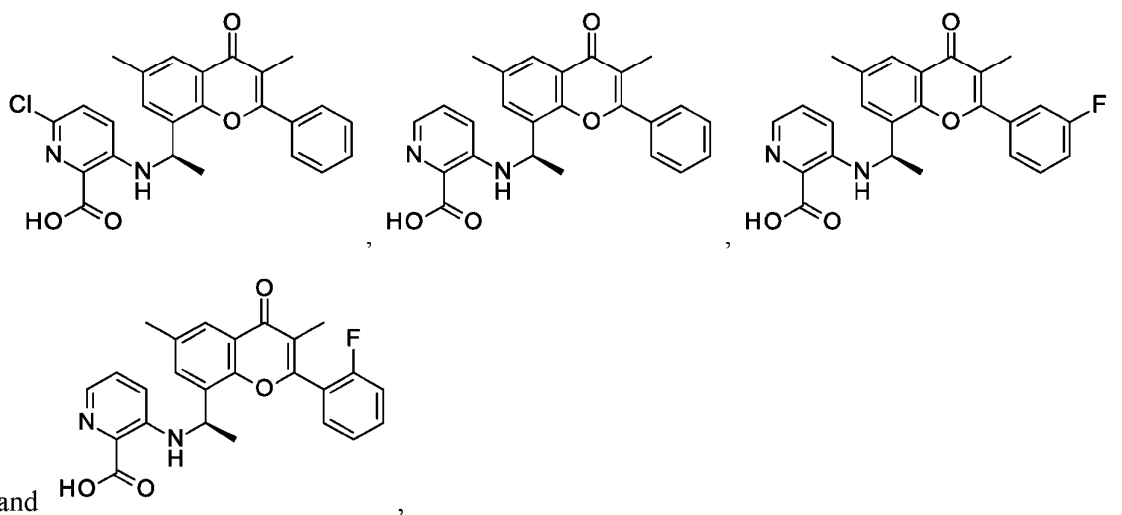
[334] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor of Formula I that is administered to the patient is of a formula:

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or a pharmaceutically acceptable salt thereof.

[335] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor of Formula I that is administered to the patient is selected from:



or a pharmaceutically acceptable salt thereof.

[336] In the disclosed methods, the patient may have a cancer comprising a mutation M1043I/L (optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g, C901F optionally in *cis* with an H1047R mutation), and the patient further may have a cancer comprising one or more mutations selected from E542K, E545K, E453Q/K, and E726K. In some aspects, the patient in need thereof may have advanced, or metastatic breast cancer which is estrogen receptor-positive (ER+),

human epidermal growth factor receptor 2-negative (HER2-).

[337] In some aspects, the disclosed methods comprise administering to the patient a therapeutically effective amount of a PI3K α selective allosteric inhibitor and the disclosed methods further comprise administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

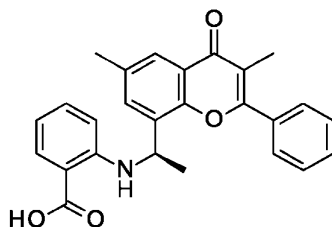
[338] I.G. Diagnosis and Treatment of Patients that Have M1043X+H1047R Cancer or C901X+H1047R Cancer

[339] In some aspects, the methods related to methods for treating a disease or disorder associated with modulation of PI3K α in a patient in need thereof, such as a patient having a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation). The methods may comprise determining that the patient has a cancer comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), for example, by ordering or performing a genomic analysis that identifies mutations in the patient's cancer (e.g., M1043I/L and/or C901F and/or H1047R, optionally in *cis*). Suitable genomic analysis may include one or more steps such as: ordering a genomic analysis that identifies the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*); performing PCR amplification of the allele comprising the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*); sequencing of the allele comprising the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*); probing of the allele comprising the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*); identifying or detecting the allele comprising the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*); and determining that a patient has a cancer comprising the M1043 mutation, the C901 mutation, and/or the H1047R mutation (optionally in *cis*). After having determined that the patient has a cancer comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), the methods further may comprise administering treatment to the patient, which

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may include administering to the patient one or more PI3K α selective inhibitors to the patient.

[340] In some aspects of the disclosed methods, if the patient has a cancer comprising an M1043 mutation (e.g., 1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor. In some aspects, the PI3K α selective inhibitor is not of a formula:



or a pharmaceutically acceptable salt thereof.

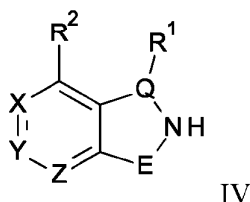
[341] In some aspects of the disclosed methods, if the patient has a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective orthosteric inhibitor. In some aspects, the PI3K α selective orthosteric inhibitor is selected from alpelisib, inavolisib, serabelisib, or pharmaceutically acceptable salts thereof.

[342] In some aspects of the disclosed methods, if the patient has a cancer comprising an M1043 mutation (M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor, wherein the PI3K α selective inhibitor binds to the PI3K α allosteric pocket 2 and may form an interaction with one or more amino acids selected from L911, F937, F1002, E1012, and D1018. In some aspects, the PI3K α selective allosteric inhibitor is a compound disclosed in WO2021/222556 (e.g., any of Compounds I-1 through I-2704 in Table 1, pages 162-855). In some aspects, the PI3K α selective allosteric inhibitor is a compound disclosed in WO2022/265993, Tables A-D, pages 175-259).

[343] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is

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administered to the patient is of a Formula IV:



or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)₂-, -C(R^E)₂C(R^E)₂-, -C(S)-, -S(O)₂-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)₂C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R¹ is -L¹-R^{1A};

R² is -L²-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R¹ are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4

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heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C} ;

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC} ; each of L^1 , L^2 , L^E , L^Q , L^X , L^Y , and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, $-N(R)-$, $-N(R)C(O)-$, $-N(R)C(NR)-$, $-N(R)C(NOR)-$, $-N(R)C(NCN)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C} ;

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$; each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic

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ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

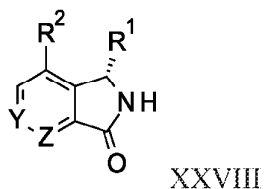
each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

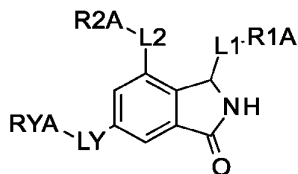
[344] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula XXVIII:

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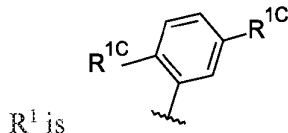
or a pharmaceutically acceptable salt thereof.

[345] In some aspects of the disclosed methods, the allosteric inhibitor is of a Formula:



or a pharmaceutically acceptable salt thereof.

[346] In some aspects, the allosteric inhibitor is of a formula in which



[347] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[348] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{1C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[349] In some aspects, the allosteric inhibitor is of a formula in which R^2 is -N(H)C(O)- R^{2A} , -N(H)C(O)N(H)- R^{2A} , -C(O)N(H)- R^{2A} , -N(H)- R^{2A} , -S(O)₂CH₂- R^{2A} , -CH₂S(O)₂- R^{2A} , or -C(H)(CH₃)OH.

[350] In some aspects, the allosteric inhibitor is of a formula in which R^{2A} is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

[351] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is

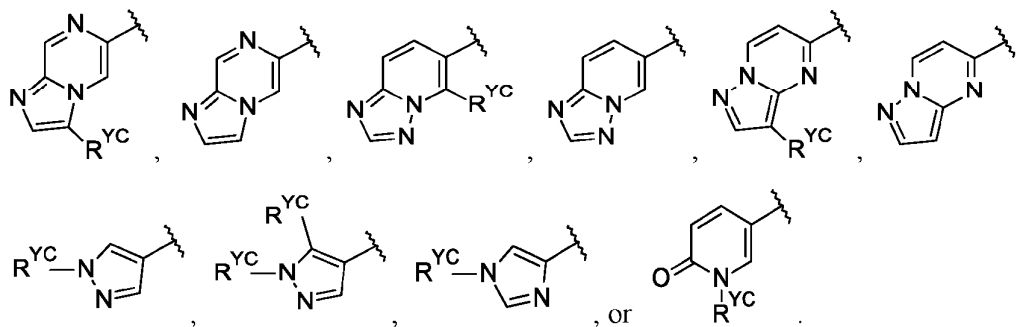
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independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

[352] In some aspects, the allosteric inhibitor is of a formula in which each instance of R^{2C} is independently halogen or C₁₋₃ aliphatic optionally substituted with 1-3 halogen.

[353] In some aspects, the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r⁶ instances of R^{YC}.

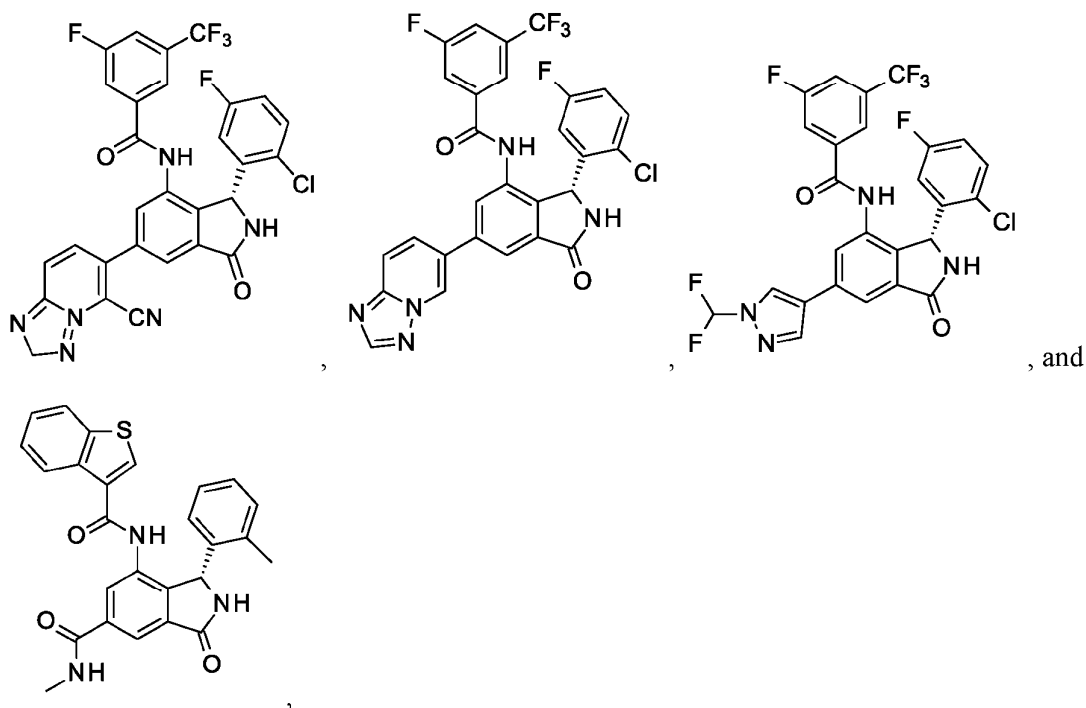
[354] In some aspects, the allosteric inhibitor is of a formula in which R^{YA} is



[355] In some aspects, the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

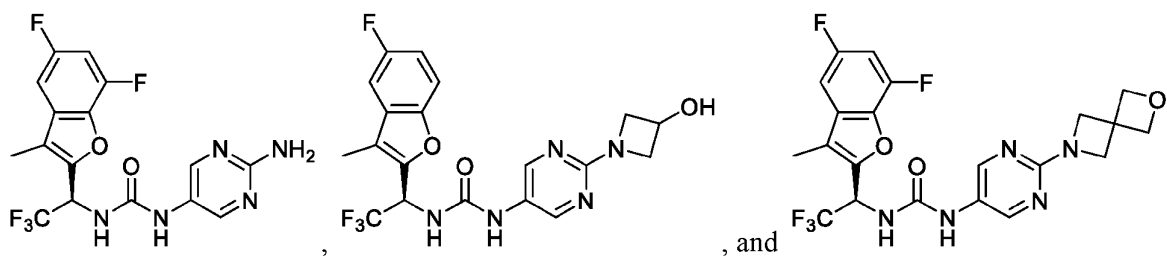
[356] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is administered to the patient is of a formula selected from:

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or pharmaceutically acceptable salts thereof.

[357] In some aspects of the disclosed methods, the second PI3K α selective inhibitor is disclosed in WO2022/265993 and has a formula selected from:



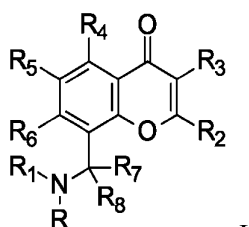
or a pharmaceutically acceptable salt thereof.

[358] In some aspects of the disclosed methods, if the patient has a cancer comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), the methods may comprise administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor that binds to the PI3K α

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allosteric pocket 1 and may form an interaction with one or more amino acids selected from C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047.

[359] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor that is administered to the patient is of a Formula I:

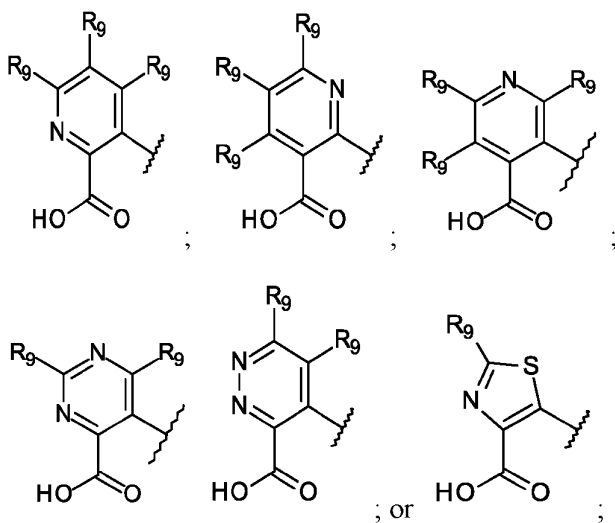


I

or pharmaceutically acceptable salt thereof, wherein:

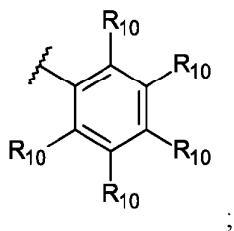
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:

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R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

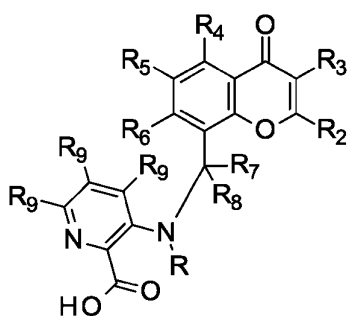
each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each

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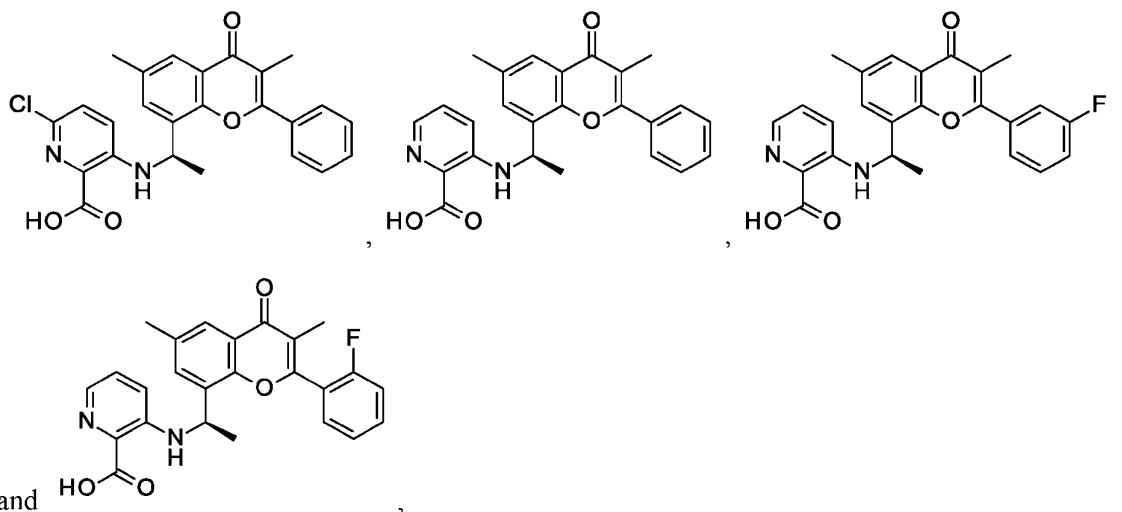
independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each R₁₁ is independently -H or C₁-C₃ alkyl.

[360] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor of Formula I is of a formula:



or a pharmaceutically acceptable salt thereof.

[361] In some aspects of the disclosed methods, the PI3K α selective allosteric inhibitor of Formula I that is administered to the patient is selected from:



or a pharmaceutically acceptable salt thereof.

[362] In some aspects of the disclosed methods, the patient may have a cancer comprising an M1043

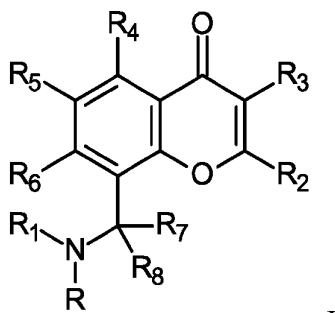
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mutation (e.g, M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation), and the patient further may have a cancer comprising one or more mutations selected from E542K, E545K, E453Q/K, and E726K. In some aspects, the patient in need thereof may have advanced, or metastatic breast cancer that is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[363] Compounds for Use in Treatment

[364] In some aspects, the disclosed subject matter relates to a first PI3K α specific inhibitor for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor. The disclosed compounds for use in treatment may be further illustrated by the following embodiments.

[365] Embodiment 1. A PI3K α specific inhibitor compound of Formula:

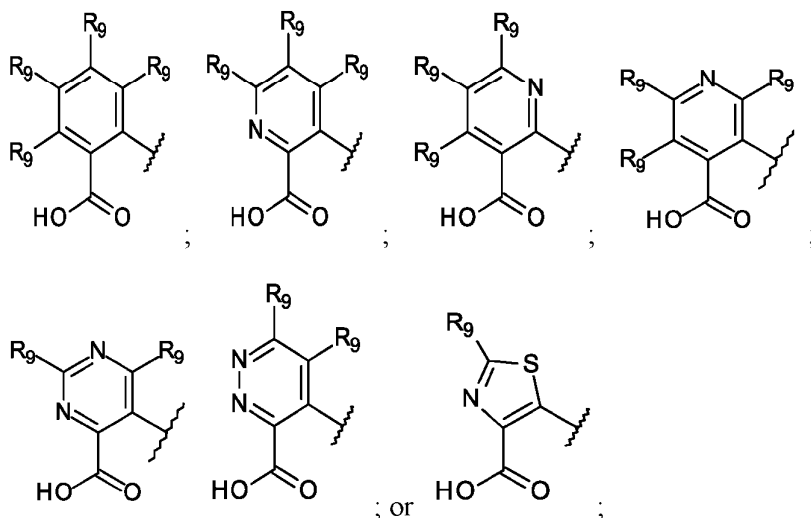


I

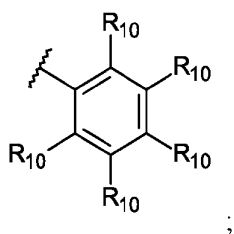
or a pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



$\mathbf{R}_2$ is a group of the formula:



R₃ is -H, halogen, -CN, -N(H)(C₁-C₃ alkyl), -N(C₁-C₃ alkyl)₂, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₅ cycloalkyl, an optionally substituted heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or an optionally substituted heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S; wherein the optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

each of **R**₄, **R**₅ and **R**₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅

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cycloalkyl;

each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, -OH, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C₁-C₃ alkoxy, or -CONR₁₁R₁₁; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R**₁₁ is independently -H or C₁-C₃ alkyl;

for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor which is a PI3K α specific orthosteric inhibitor.

[366] Embodiment 2. A compound for use according to embodiment 1, wherein the second PI3K α specific inhibitor is alpelisib or a pharmaceutically acceptable salt thereof.

[367] Embodiment 3. A compound for use according to embodiment 1, wherein the second PI3K α specific inhibitor is inavolisib or a pharmaceutically acceptable salt thereof.

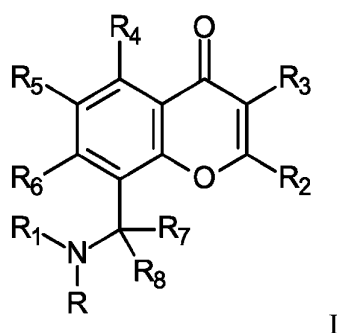
[368] Embodiment 4. A compound for use according to any of embodiments 1-3, wherein the dose of the second PI3K α specific inhibitor is less than about a 300 mg oral dose administered every day.

[369] Embodiment 5. A compound for use according to any of embodiments 1-4, wherein the first PI3K α specific inhibitor and the second PI3K α specific inhibitor are administered simultaneously.

[370] Embodiment 6. A compound for use according to embodiment 5, wherein the dose of the second PI3K α specific inhibitor is less than about a 50, 30, 12.5, 6.25, or 3.125 mg/kg oral dose administered every day.

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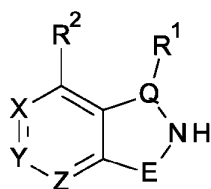
[371] Embodiment 7. A PI3K α specific inhibitor compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in embodiment 1; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor which binds to PI3K α allosteric pocket 2.

[372] Embodiment 8. The compound for use according to embodiment 7, wherein the second PI3K α specific inhibitor forms one or more interactions with one or more amino acids selected from L911, F937, F1002, E1012, and D1018.

[373] Embodiment 9. The compound for use according to embodiment 7 or 8, wherein the second PI3K α specific inhibitor is of a formula:



or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)₂-, -C(R^E)₂C(R^E)₂-, -C(S)-, -S(O)₂-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)₂C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

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Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R^I is -L^I-R^{IA};

R² is -L²-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R^I are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{QIC};

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC}; each of L^I, L², L^E, L^Q, L^X, L^Y, and L^Z is independently a covalent bond, or a C₁₋₄ bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-, -C(R^L)₂-, C₃₋₆ cycloalkylene, C₃₋₆ heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, -N(R)S(O)₂-, -S(O)₂N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, or -S(O)₂-;

R^{IA} is R^A or R^B substituted by r^I instances of R^{IC};

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R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C} ;

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC} ;

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC} ;

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC} ;

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC} ;

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC} ;

R^L is R^A or R^B substituted by r^8 instances of R^{LC} ;

each instance of R^A is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -S(O)(NCN)R, -S(NCN)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, or -B(OR)₂;

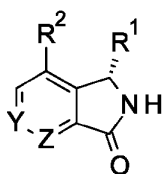
each instance of R^B is independently a C₁₋₆ aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^{1C} , R^{2C} , R^{EC} , R^{QC} , R^{XC} , R^{YC} , R^{ZC} , R^{LC} , R^{EEC} , R^{Q1C} , and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO₂, -OR, -SF₅, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)₂F, -S(O)R, -S(O)NR₂, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, -P(O)R₂, -P(O)(R)OR, -B(OR)₂, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from

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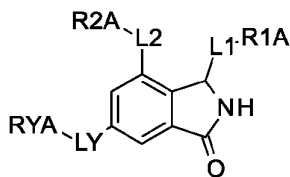
nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic (wherein the C₁₋₆ aliphatic group is optionally substituted at one or more positions with substituents selected from C₁₋₃ alkyl, C₁₋₃ haloalkyl, and halogen), phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and each of n, p, q, r¹, r², r³, r⁴, r⁵, r⁶, r⁷, and r⁸ is independently 0, 1, 2, 3, 4, or 5.

[374] Embodiment 10. The compound for use according to any of embodiments 7-9, wherein the second PI3K α selective inhibitor is of a formula:



or a pharmaceutically acceptable salt thereof.

[375] Embodiment 11. The compound for use according to any of embodiments 7-10, wherein the second PI3K α selective inhibitor is of a formula:

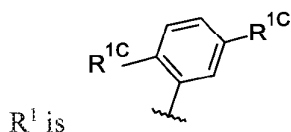


or a pharmaceutically acceptable salt thereof.

[376] Embodiment 12. The compound for use according to any of embodiments 7-11, wherein

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the second PI3K α selective inhibitor is of a formula in which



[377] Embodiment 13. The compound for use according to any of embodiments 7-12, wherein the second PI3K α selective inhibitor is of a formula in which each instance of R^{1C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

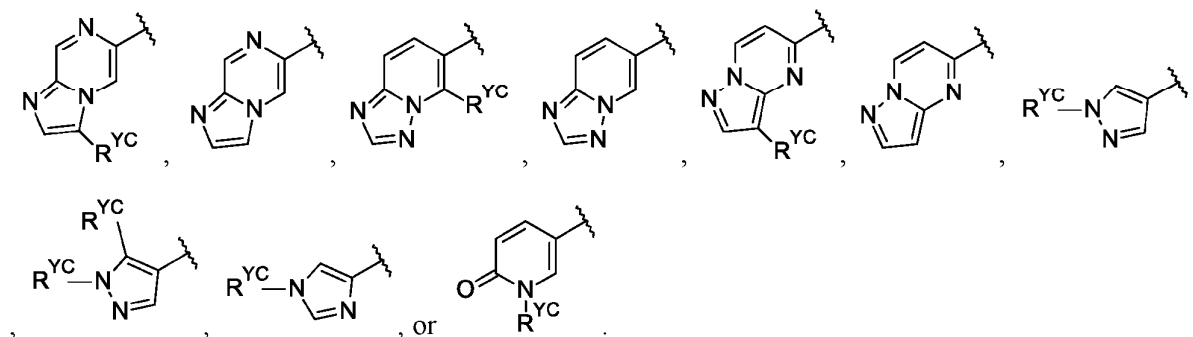
[378] Embodiment 14. The compound for use according to any of embodiments 7-13, wherein the second PI3K α selective inhibitor is of a formula in which R^2 is -N(H)C(O)- R^{2A} , -N(H)C(O)N(H)- R^{2A} , -C(O)N(H)- R^{2A} , -N(H)- R^{2A} , -S(O)₂CH₂- R^{2A} , -CH₂S(O)₂- R^{2A} , or -C(H)(CH₃)OH.

[379] Embodiment 15. The compound for use according to any of embodiments 7-14, wherein the second PI3K α selective inhibitor is of a formula in which R^{2A} is phenyl optionally substituted at one or more positions C₁₋₃ aliphatic (*e.g.*, methyl), haloalkyl (*e.g.*, trifluoromethyl or difluoromethyl), or halogen.

[380] Embodiment 16. The compound for use according to any of embodiments 7-15, wherein the second PI3K α selective inhibitor is of a formula in which each instance of R^{2C} is independently halogen, -CN, -O-(C₁₋₆ aliphatic), or C₁₋₆ aliphatic; wherein each C₁₋₆ aliphatic is optionally substituted with one or more halogen atoms.

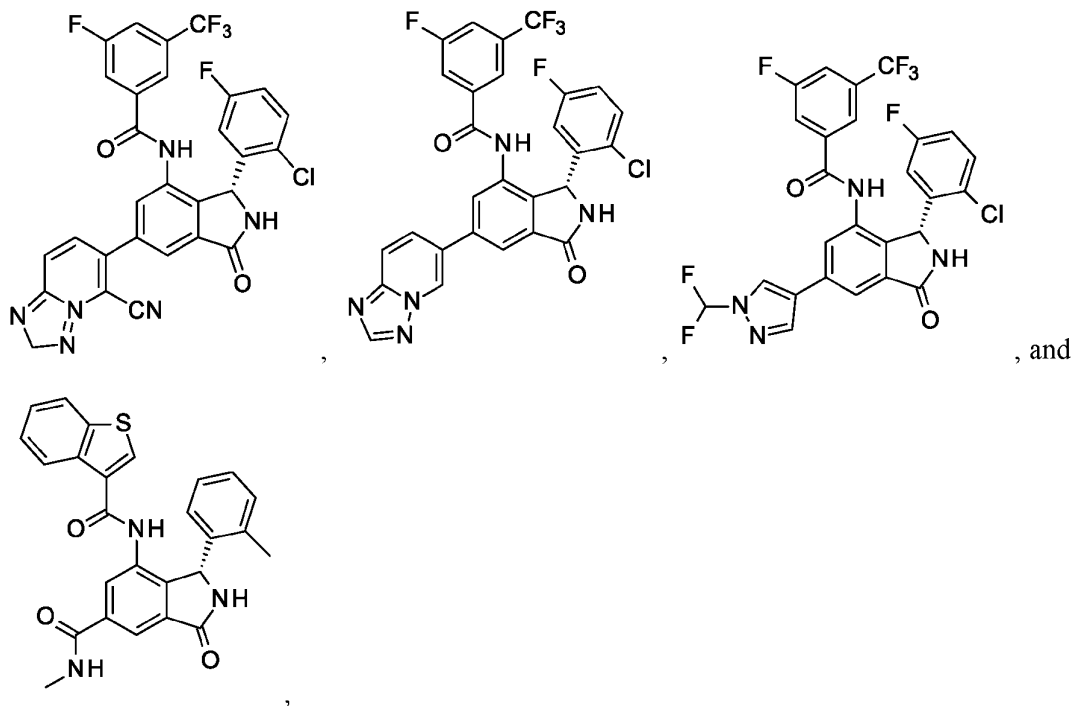
[381] Embodiment 17. The compound for use according to any of embodiments 7-16, wherein the second PI3K α selective inhibitor is of a formula in which R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r^6 instances of R^{YC} .

[382] Embodiment 18. The compound for use according to any of embodiments 7-17, wherein the second PI3K α selective inhibitor is of a formula in which R^{YA} is



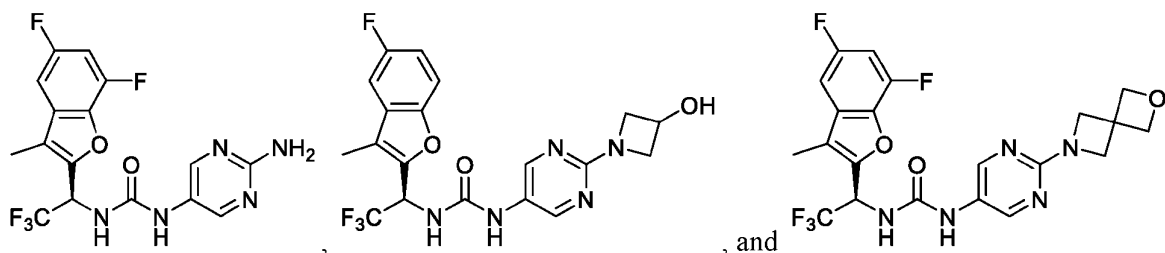
[383] Embodiment 19. The compound for use according to any of embodiments 7-18, wherein the second PI3K α selective inhibitor is of a formula in which each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C₁₋₃ aliphatic), or C₁₋₃ aliphatic, wherein each C₁₋₃ aliphatic is optionally substituted with one or more halogen atoms.

[384] Embodiment 20. The compound for use according to embodiment 19, wherein the second PI3K α selective inhibitor has a formula selected from:



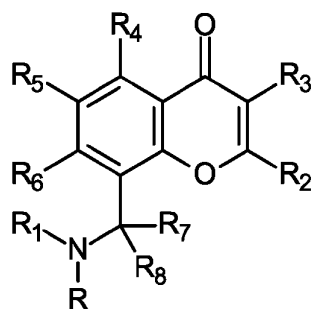
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[385] or pharmaceutically acceptable salts thereof, or the second PI3K α selective inhibitor has a formula selected from:



or pharmaceutically acceptable salts thereof.

[386] Embodiment 21. A PI3K α specific inhibitor compound of Formula I:

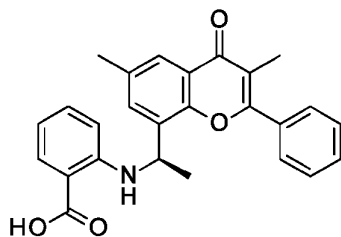


I

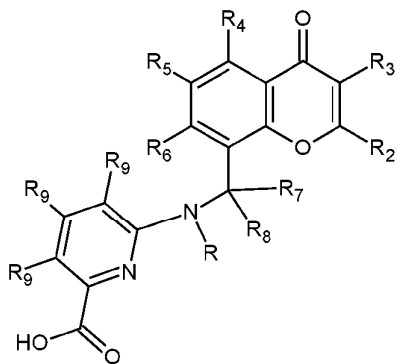
or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 1; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor of Formula I or pharmaceutically acceptable salt thereof, wherein the first PI3K α specific inhibitor and the second PI3K α specific inhibitor are different compounds.

[387] Embodiment 22. A compound for use according to embodiment 21, wherein the second PI3K α specific inhibitor is not of a formula:

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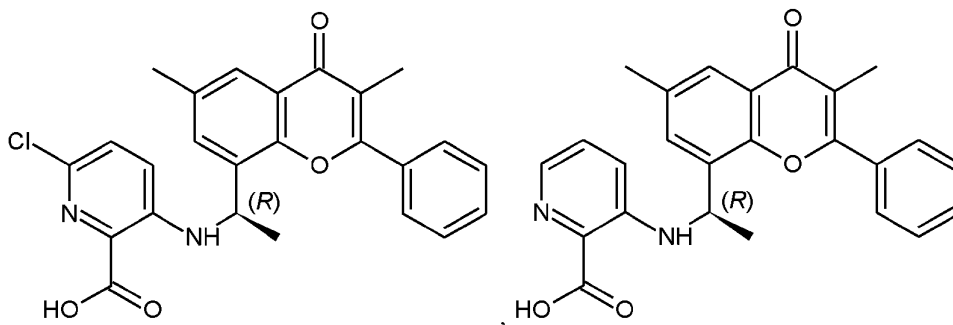


[388] Embodiment 23. A compound for use according to embodiment 21 or 22, wherein the second PI3K α specific inhibitor is of a formula:

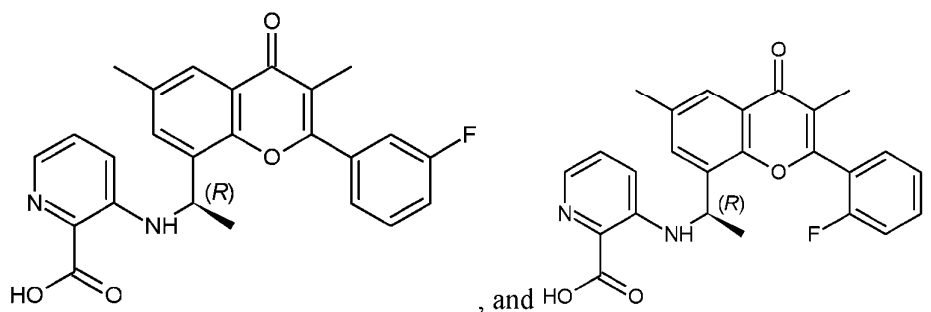


or a pharmaceutically acceptable salt thereof.

[389] Embodiment 24. A compound for use according to any of embodiments 21-23, wherein the second PI3K α specific inhibitor is of a formula selected from:



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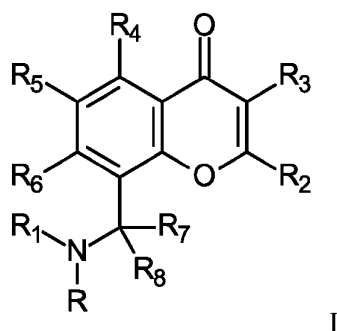


or a pharmaceutically acceptable salt thereof.

[390] Embodiment 25. A compound for use according to any of embodiments 1-24, wherein the therapeutically effective amount of the first PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

[391] Embodiment 26. A compound for use according to any of embodiments 1-25, wherein the therapeutically effective amount of the second PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

[392] Embodiment 27. A PI3K α specific inhibitor compound of a Formula I:



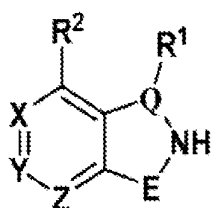
or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in embodiment 1; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), of a patient that is resistant to treatment with alpelisib or inavolisib.

[393] Embodiment 28. A PI3K α specific inhibitor which binds to an allosteric pocket of PI3K α and optionally forms one or more interactions with one or more amino acids selected from

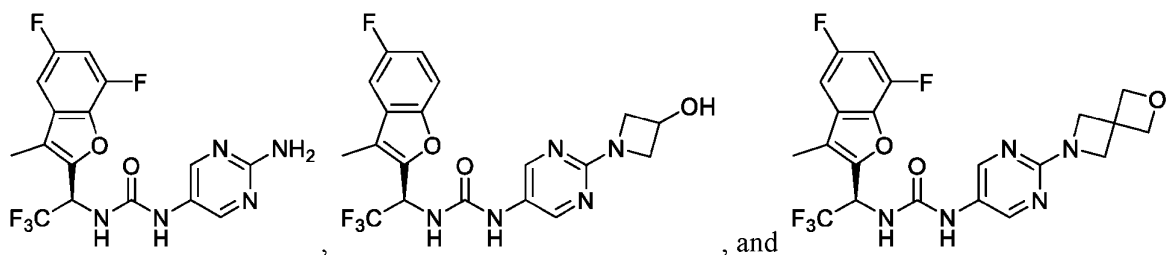
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L911, F937, F1002, E1012, and D1018 for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), of a patient that is resistant to treatment with alpelisib or inavolisib.

[394] Embodiment 29. A PI3K α specific inhibitor for use according to embodiment 28, wherein said inhibitor is a compound of Formula :



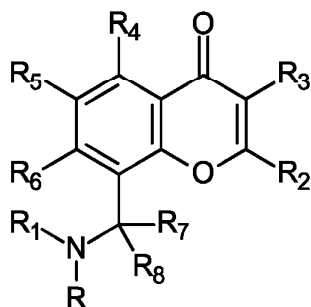
or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, E, Q, X, Y, Z are as defined in embodiment 9, or a PI3K α specific inhibitor for use according to embodiment 28, wherein said inhibitor is a compound of Formula selected from:



or a pharmaceutically acceptable salt thereof.

[395] Embodiment 30. A PI3K α specific inhibitor which is a PI3K α specific orthosteric inhibitor for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), wherein the patient has been treated previously with compound of Formula I

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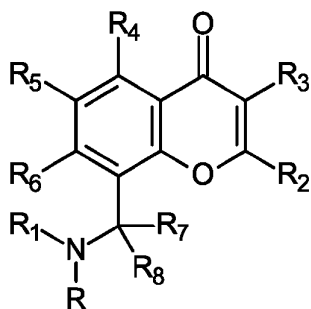


I

or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in embodiment 96, and the patient has a cancer which has acquired an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

[396] Embodiment 31. A PI3K α specific inhibitor that binds to PI3K α allosteric pocket 2 and optionally forms one or more interactions with one or more amino acids selected from L911, F937, F1002, E1012, and D1018 for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

[397] Embodiment 32. A PI3K α specific inhibitor compound of Formula I:



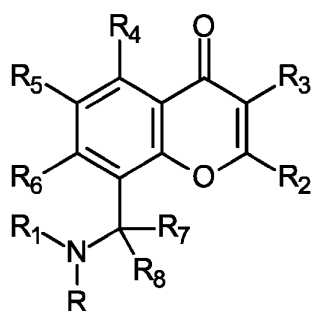
I

or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in embodiment 1, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the

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patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

[398] Embodiment 33. A PI3K α specific inhibitor compound of Formula I:



I

or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in embodiment 1, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a blood sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of compound of Formula I or pharmaceutically acceptable salt thereof to the patient if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present.

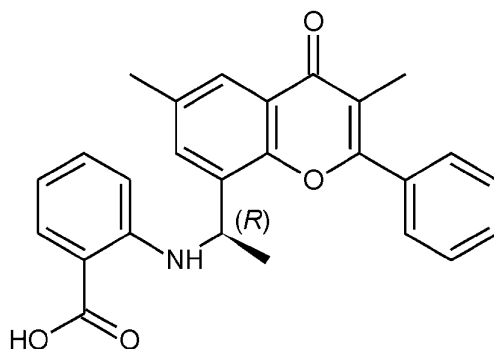
[399] Embodiment 34. A PI3K α specific inhibitor selected from alpelisib and inavolisib, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of alpelisib, inavolisib, or a pharmaceutically acceptable salt thereof to the patient if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present.

[400] Embodiment 35. A PI3K α specific inhibitor that binds to PI3K α allosteric pocket 2 and optionally forms one or more interactions with one or more amino acids selected from L911, F937,

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F1002, E1012, and D1018, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a blood sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of the PI3K α specific inhibitor or pharmaceutically acceptable salt thereof to the patient if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present.

[401] Embodiment 36. A compound for use according to any one of embodiments 1-27, 30, 32, and 33, wherein the compound of Formula I is of the formula:



or a pharmaceutically acceptable salt thereof.

[402] Embodiment 37. A compound for use according to any one of embodiments 1-27, 30, 32, and 33, wherein the therapeutically effective amount of the compound of Formula I administered to the patient is a 100-1200 mg oral dose administered two times daily.

[403] Embodiment 38. A compound for use according to any one of embodiments 1-27, 30, 32, and 33, wherein the therapeutically effective amount of the first PI3K α specific inhibitor administered to the patient is a 9-75 mg/kg oral dose administered two times daily.

[404] Embodiment 39. A compound for use according to any of embodiments 1-38, wherein the disease or disorder is cancer.

[405] Embodiment 40. A compound for use according to any of embodiments 1-39, wherein the disease or disorder is breast cancer.

[406] Embodiment 41. A compound for use according to any of embodiments 1-40, wherein the disease or disorder is PIK3CA-mutated, advanced, or metastatic breast cancer.

[407] Embodiment 42. A compound for use according to any of embodiments 1-41, wherein the disease or disorder is PIK3CACA H1047R-mutant advanced, or metastatic breast cancer.

[408] Embodiment 43. A compound for use according to embodiment 42, wherein the PIK3CACA H1047R-mutant advanced, or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[409] Embodiment 44. A compound for use according to any of embodiments 1-43, wherein the patient is a postmenopausal female.

[410] Embodiment 45. A compound for use according to any of embodiments 1-44, wherein the patient has type II diabetes mellitus.

[411] Embodiment 46. A compound for use according to any of embodiments 1-45, further comprising administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

[412] Embodiment 47. A compound for use according to embodiment 46, wherein the SERD is selected from imlunestrant, fulvestrant, giredestrant, amcenestrant, rintodestrant, elacestrant, camizestrant, LSZ102, Zn-c5, and D-0502.

[413] Embodiment 48. A compound for use according to embodiment 46 or 47, wherein the therapeutically effective amount of the SERD is a 500 mg dose administered on days 1, 15, and 29.

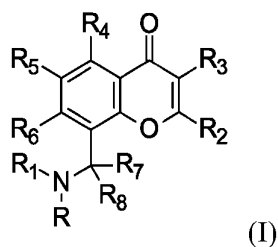
[414] Embodiment 49. A compound for use according to any one of embodiments 1-48, wherein the second PI3K α specific inhibitor is administered after the disease or disorder has developed resistance to the first PI3K α specific inhibitor.

[415] Illustrative Compounds

[416] The following are illustrative compounds that may be used in some aspects of the disclosed subject matter.

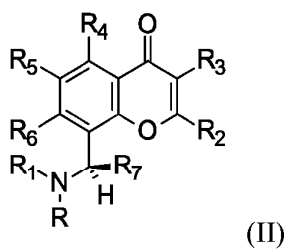
[417] In one aspect, the present invention provides compounds of Formula (I), or pharmaceutically acceptable salts thereof:

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wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in the Summary for Formula (I).

[418] In a further aspect, compounds of Formula (I) wherein **R₈** is H have Formula (II), or pharmaceutically acceptable salts thereof:

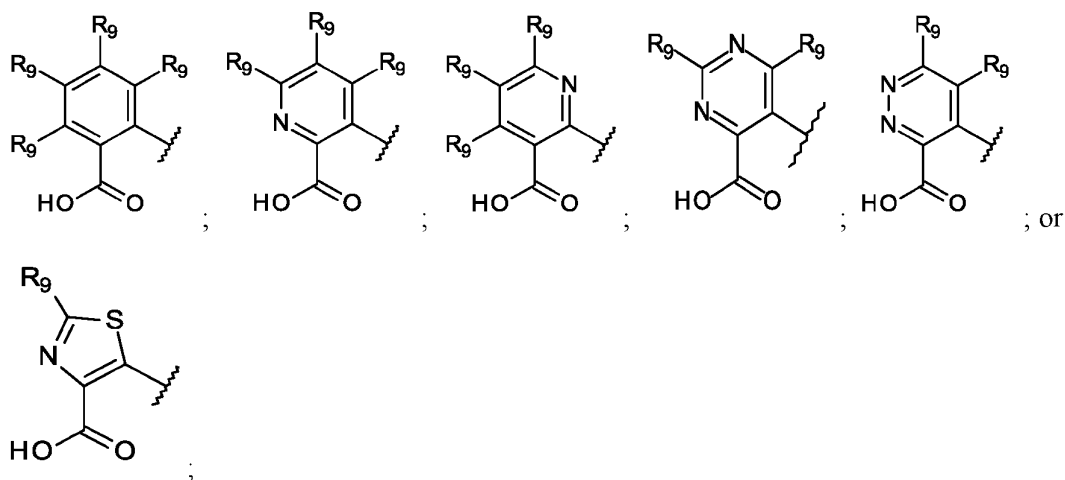


wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, and **R₇**, are as defined in the Summary for Formula (I).

[419] In a compound of Formula (I), or pharmaceutically acceptable salts thereof,

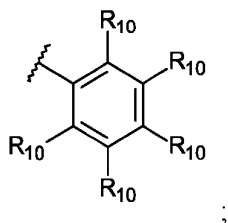
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

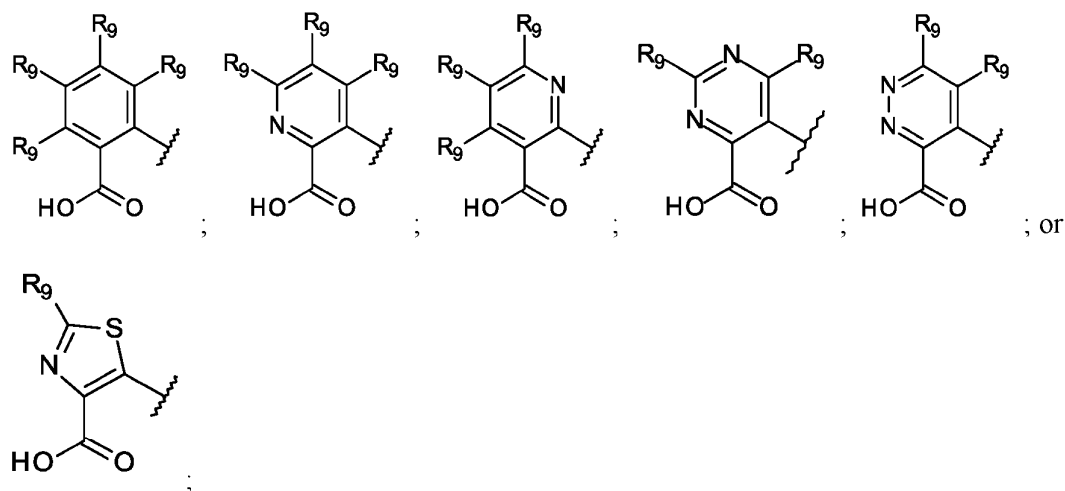
each **R₁₁** is independently -H or C₁-C₃ alkyl

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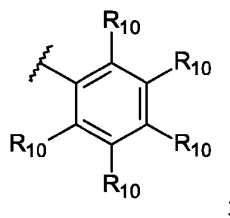
[420] In a compound of Formula (I), or pharmaceutically acceptable salts thereof,

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from

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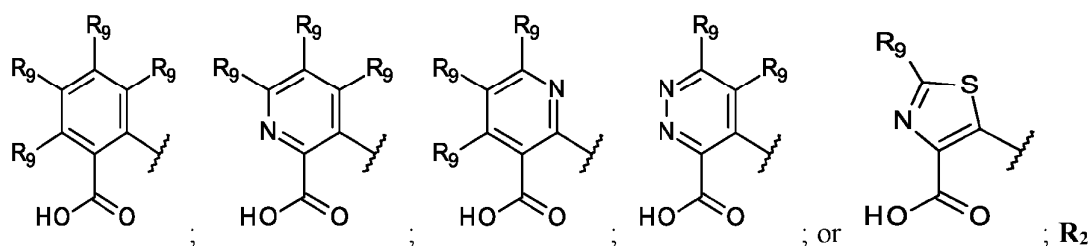
pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and

each **R**₁₁ is independently -H or C₁-C₃ alkyl

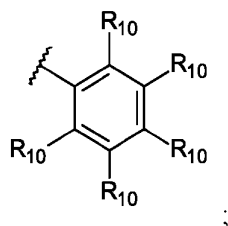
[421] In a compound of Formula (I), or pharmaceutically acceptable salts thereof,

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



is a group of the formula:



R₃ is -H, -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

each of **R**₄, **R**₅ and **R**₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

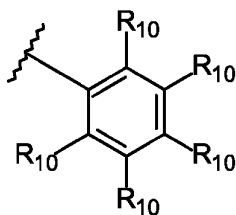
each **R**₉ is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

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each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and

each **R**₁₁ is independently -H or C₁-C₃ alkyl.

[422] In a compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:

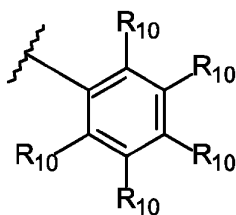


wherein each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl,

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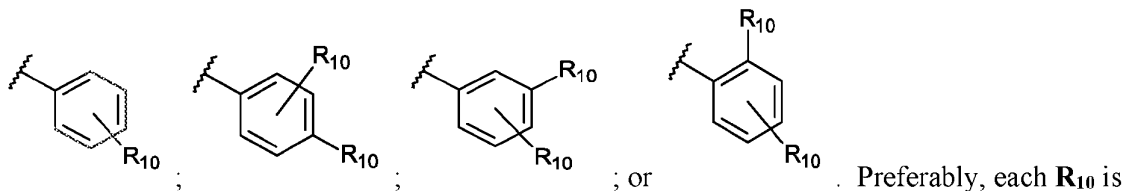
phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN.

[423] In a compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



wherein each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R**₁₁ is independently -H or C₁-C₃ alkyl.

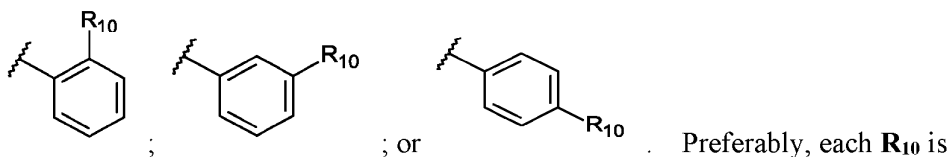
[424] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



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independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[425] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[426] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, or an

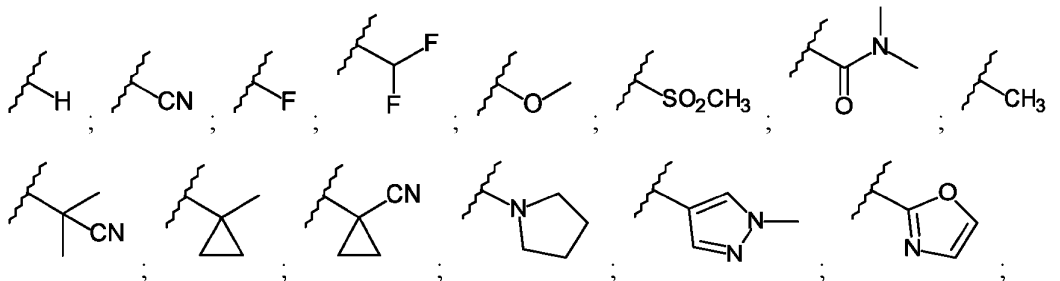
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optionally substituted heteroaryl selected from selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; and the optionally substituted C₃-C₅ cycloalkyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

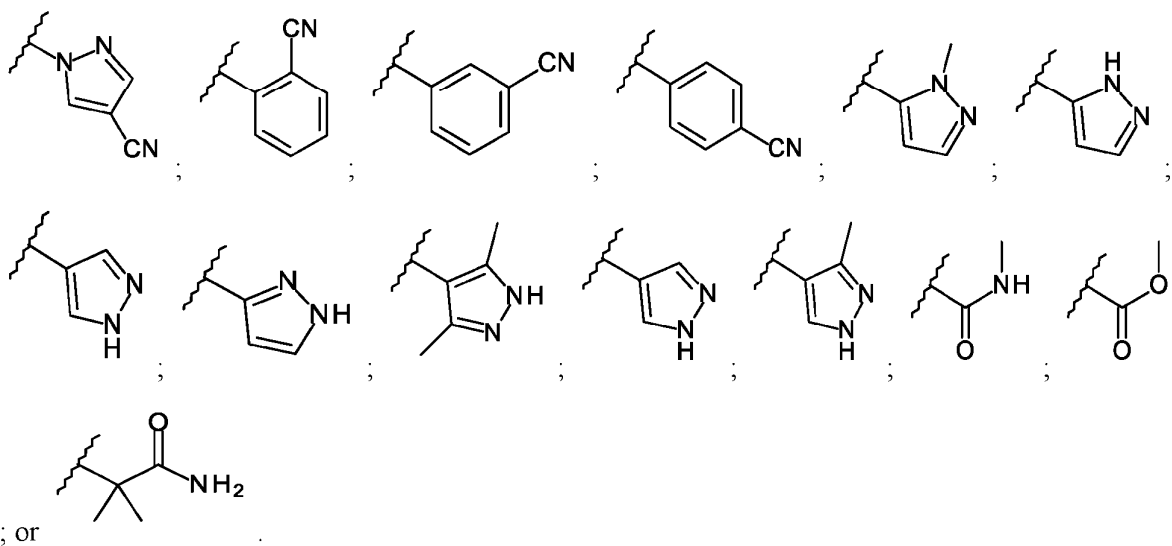
[427] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -SO₂R₁₁, -C(O)OC₁-C₃ alkyl, -CONR₁₁R₁₁, a C₁-C₆ alkyl optionally substituted with -CN or -CONR₁₁R₁₁ (preferably each **R**₁₁ is C₁-C₃ alkyl), a C₃ cycloalkyl optionally substituted with C₁-C₃ alkyl or -CN, an optionally substituted heterocycle selected from pyrrolidine, an optionally substituted phenyl (preferably an optionally substituted phenyl substituted by a -CN), or an optionally substituted heteroaryl selected from pyrazole or oxazole.

[428] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, a C₁-C₆ alkyl optionally substituted with -CN, a C₃ cycloalkyl optionally substituted with C₁-C₃ alkyl or -CN, an optionally substituted heterocycle selected from pyrrolidine, or an optionally substituted heteroaryl selected from pyrazole or oxazole.

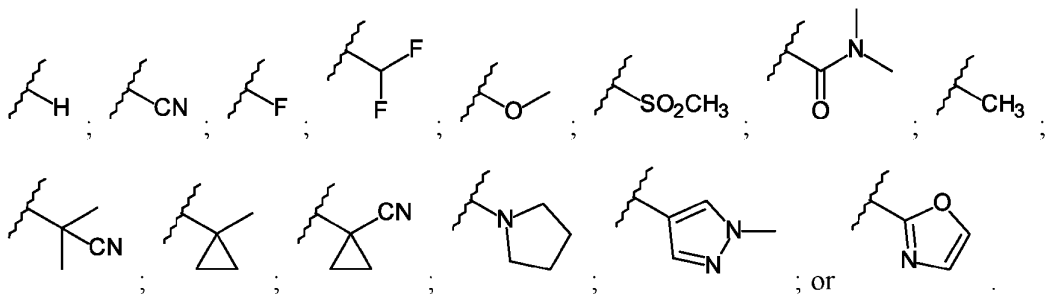
[429] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, each **R**₁₀ is independently



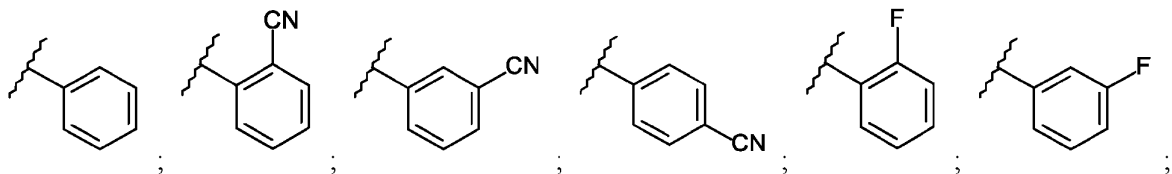
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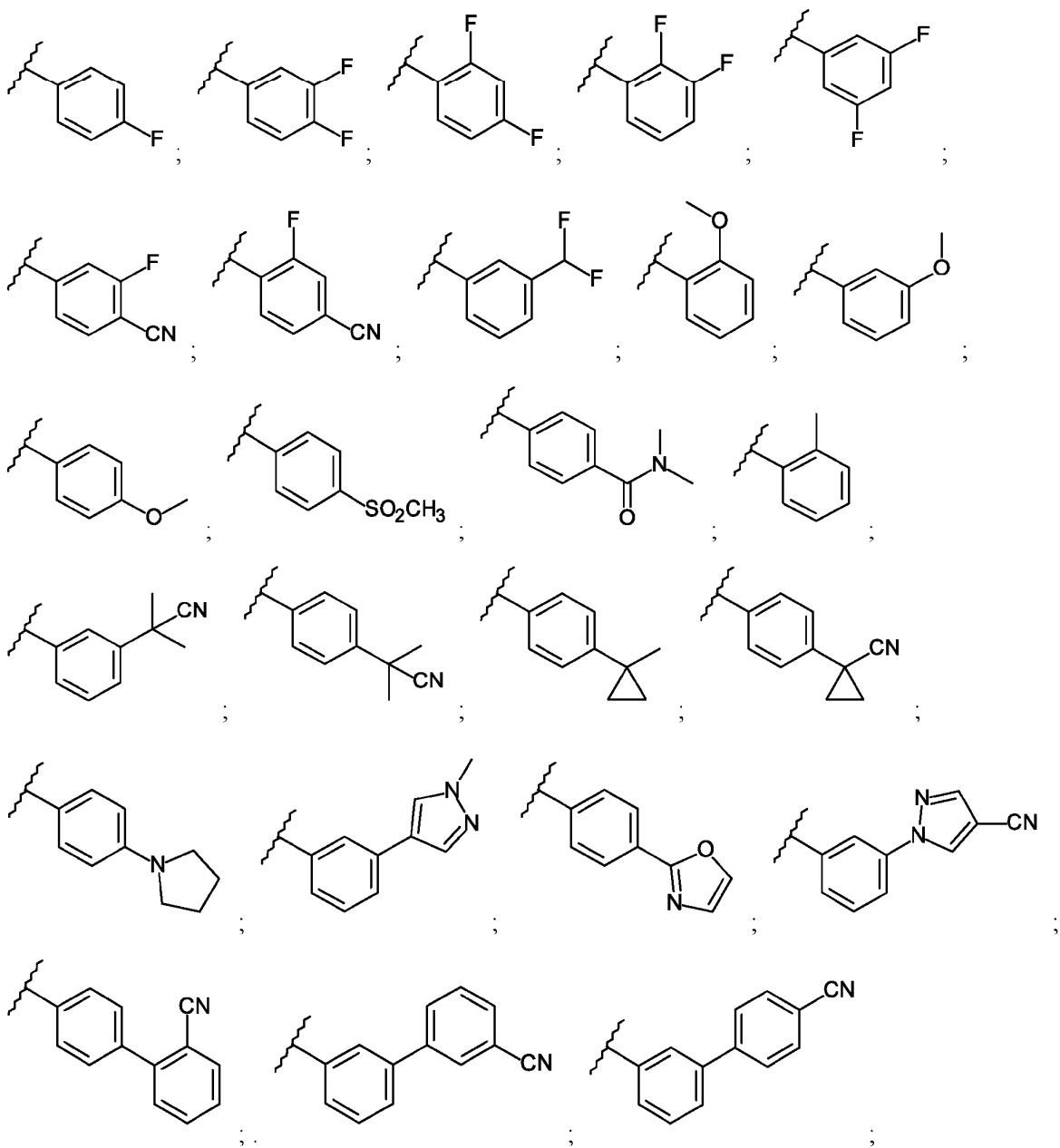
[430] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, each **R₁₀** is independently



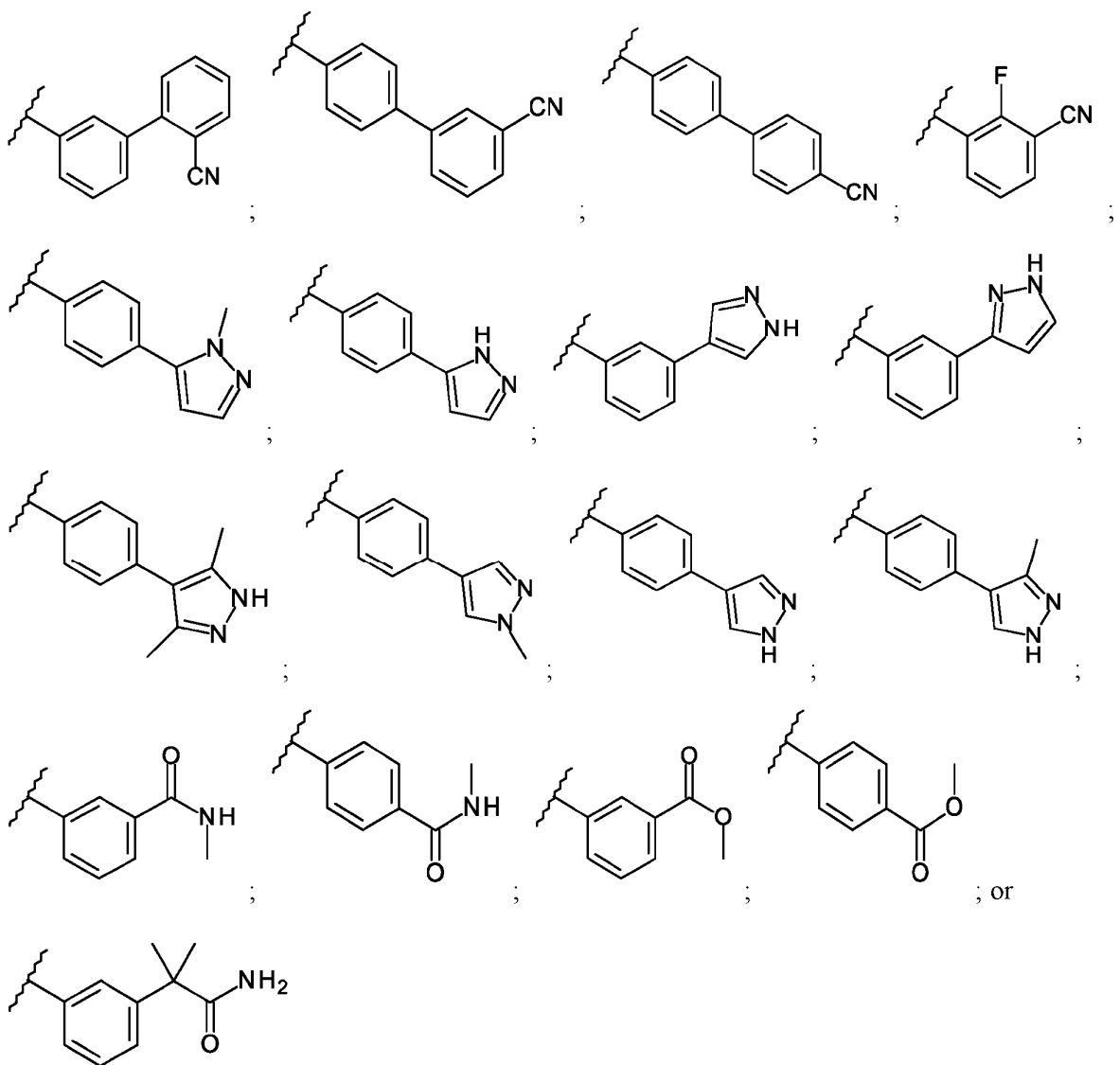
[431] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



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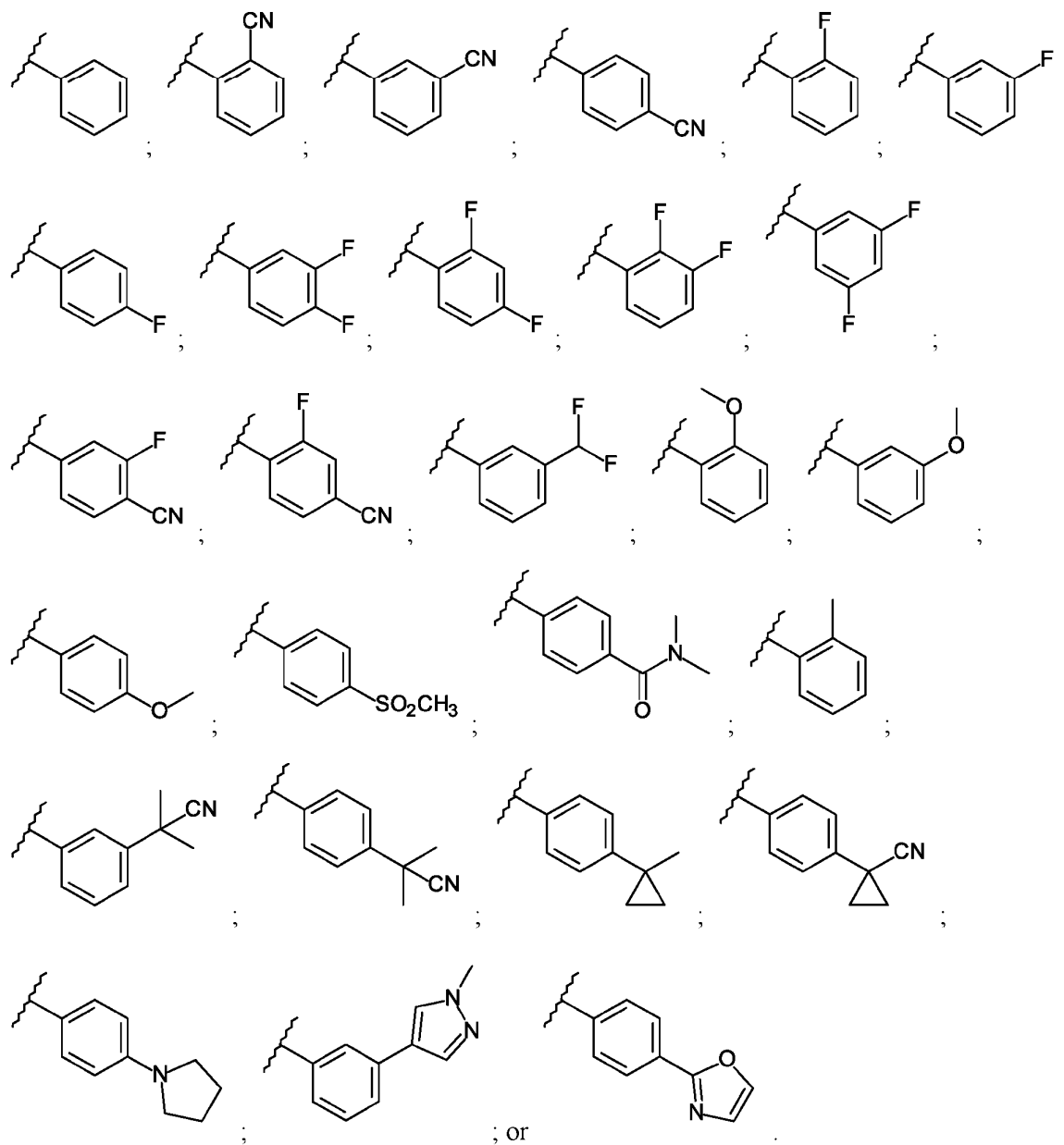


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[432] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:

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[433] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, halogen, -CN, -N(H)(CH₂CH₂CO₂H), -C(O)C₁-C₃ alkyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, oxetane, isoxazole, or pyridine (preferably 3-pyridine). In yet a further compound of Formula (I), or

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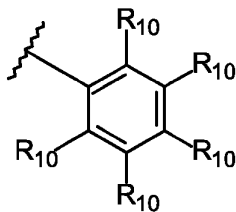
(II), or pharmaceutically acceptable salts thereof, **R₃** is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, oxetane, or isoxazole. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl); most preferably **R₃** is -H, or methyl.

[434] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₄** is H or halogen, preferably **R₄** is H.

[435] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; preferably **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R₅** is -H, halogen, methyl, or trifluoromethyl.

[436] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₆** is -H, or halogen.

[437] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), and **R₂** is a group of the formula:

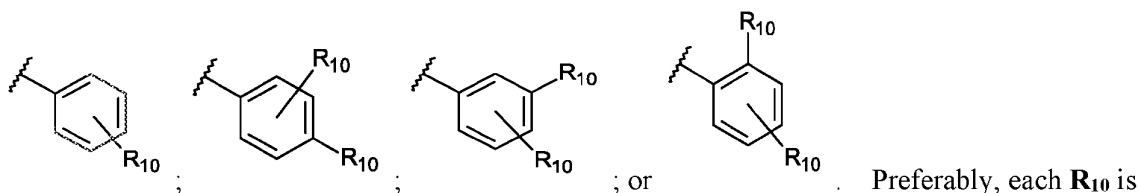


wherein each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

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haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with a $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_3$ alkoxy; the optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy, $-\text{NR}_{11}\text{R}_{11}$, $-\text{OH}$ or $-\text{CN}$; and each R_{11} is independently $-\text{H}$ or $\text{C}_1\text{-C}_3$ alkyl.

[438] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is $-\text{H}$, $-\text{CN}$, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ haloalkyl (preferably R_3 is $-\text{H}$, $-\text{CN}$, or $\text{C}_1\text{-C}_3$ alkyl), and R_2 is a group of the formula:

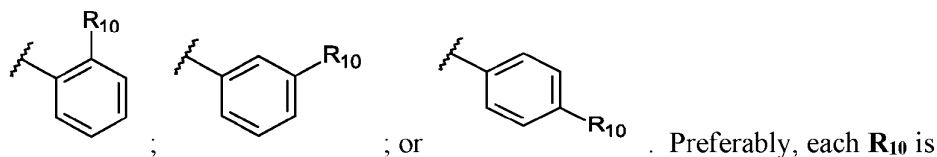


independently $-\text{H}$, $-\text{CN}$, halogen, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with a $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_3$ alkoxy; the optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy, $-\text{NR}_{11}\text{R}_{11}$, $-\text{OH}$ or $-\text{CN}$.

[439] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is $-\text{H}$, methyl or trifluoromethyl (preferably R_3 is $-\text{H}$, or methyl), and R_2 is a group of the

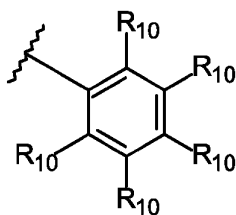
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formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[440] In a compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₄ is -H or halogen (preferably **R**₄ is -H), and **R**₂ is a group of the formula:

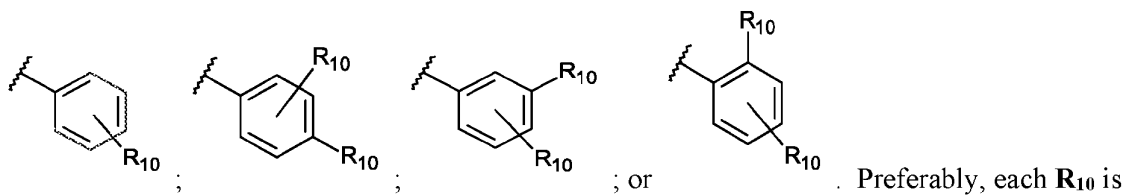


wherein each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH,

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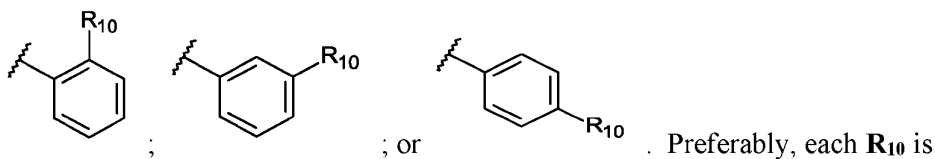
or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each R₁₁ is independently -H or C₁-C₃ alkyl.

[441] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R₄ is -H or halogen (preferably R₄ is -H), and R₂ is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[442] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R₄ is -H or halogen (preferably R₄ is -H), and R₂ is a group of the formula:

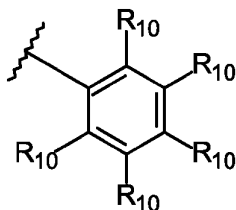


independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from

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pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

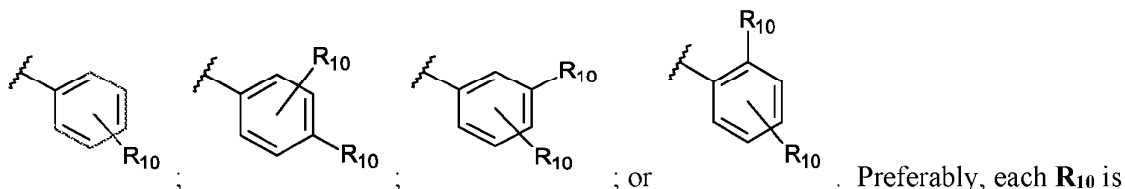
[443] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and **R₂** is a group of the formula:



wherein each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

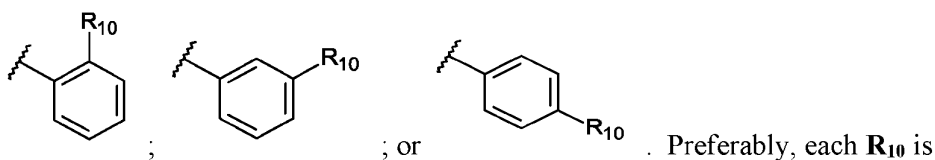
[444] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:

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Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

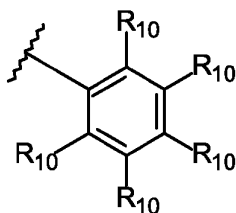
[445] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_5 is -H, halogen, methyl, or trifluoromethyl, and R_2 is a group of the formula:



Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

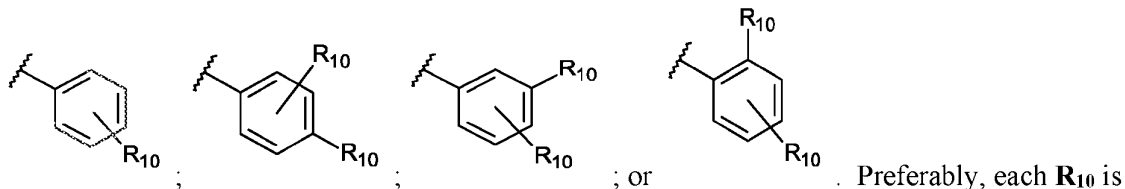
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[446] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₆** is -H, or halogen, and **R₂** is a group of the formula:



wherein each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[447] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₆** is -H, or halogen, and **R₂** is a group of the formula:

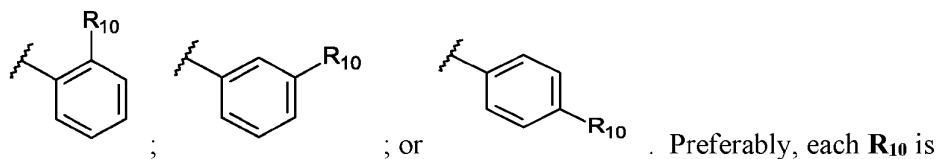


independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from

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pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[448] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₆ is -H, or halogen, and **R**₂ is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[449] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₄ is H or halogen; more preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl, and **R**₄ is H; most preferably **R**₃ is -H, or methyl, and **R**₄ is H.

[450] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), and **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R**₃ is -H, or methyl, and **R**₅ is -H, halogen, methyl, or trifluoromethyl.

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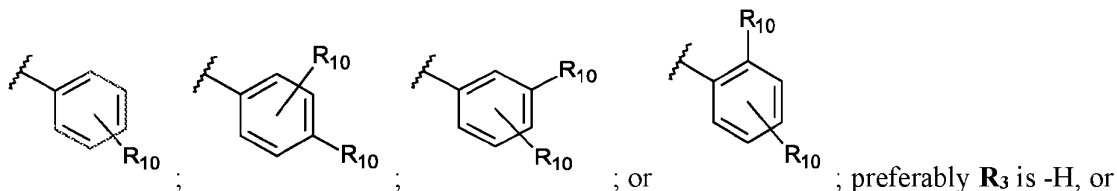
[451] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), and **R₆** is -H, or halogen; more preferably **R₃** is -H, or methyl, and **R₆** is -H, or halogen.

[452] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₄** is -H or halogen (preferably **R₄** is -H), and **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably **R₅** is -H, halogen, methyl, or trifluoromethyl.

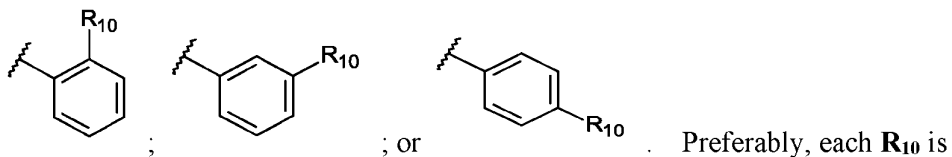
[453] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₄** is -H or halogen (preferably **R₄** is -H) and **R₆** is -H, or halogen.

[454] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₆** is -H, or halogen; preferably **R₅** is -H, halogen, methyl, or trifluoromethyl, and **R₆** is H.

[455] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₄** is -H or halogen (preferably **R₄** is -H), and **R₂** is a group of the formula:



methyl, **R₄** is -H, and **R₂** is a group of the formula:

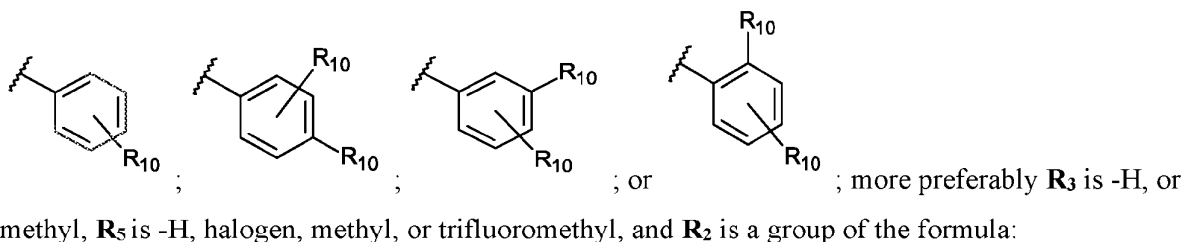
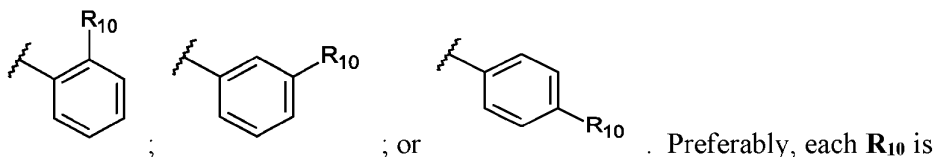


independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole,

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or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

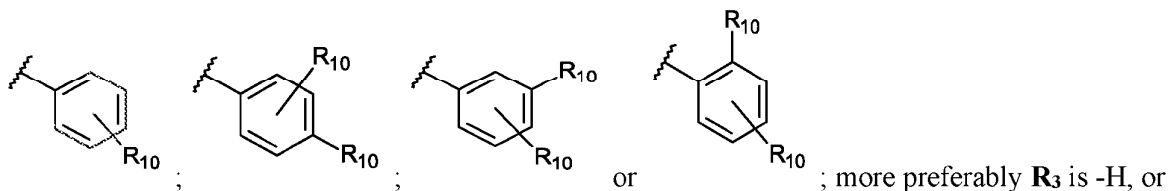
[456] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), **R**₅ is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and **R**₂ is a group of the formula:



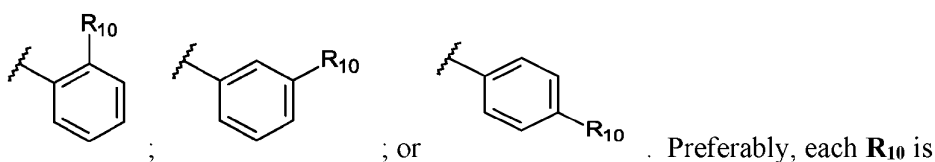
independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[457] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), **R**₆ is -H, or halogen, and **R**₂ is a group of the formula:

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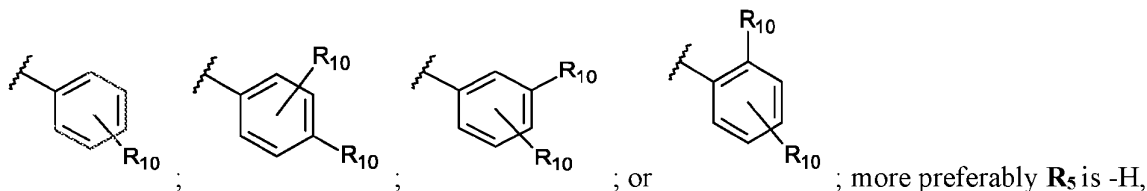


methoxy, R_6 is -H, and R_2 is a group of the formula:



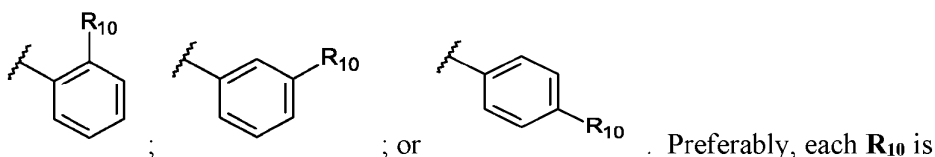
independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[458] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_4 is -H or halogen (preferably R_4 is -H), R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and R_2 is a group of the formula:



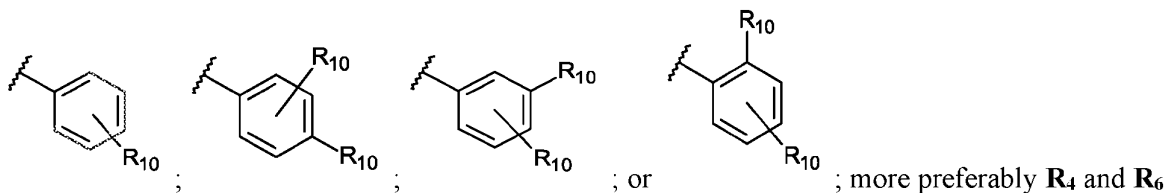
halogen, methyl, or trifluoromethyl, and R_2 is a group of the formula:

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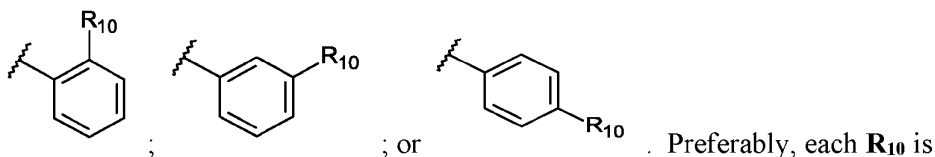


Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[459] In a compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_4 is -H or halogen (preferably R_4 is -H), R_6 is -H, or halogen, and R_2 is a group of the formula:



are each -H, and R_2 is a group of the formula:

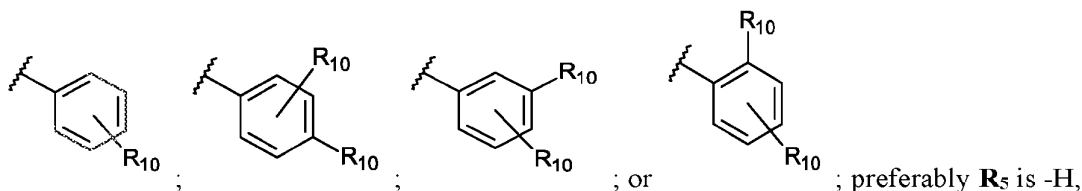


Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an

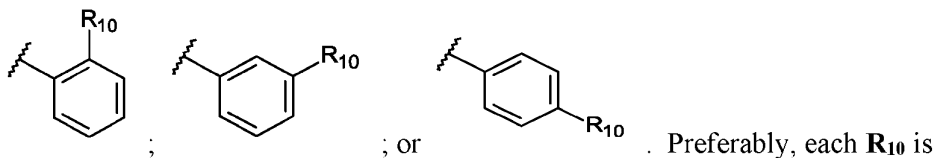
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optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[460] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H, or halogen, and **R₂** is a group of the formula:



halogen, methyl, or trifluoromethyl, **R₆** is -H, and **R₂** is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[461] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₄** is -H or

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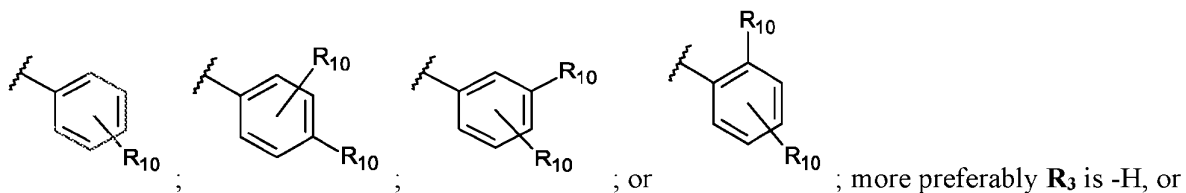
halogen (preferably **R₄** is -H), and **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R₃** is -H, or methyl, **R₄** is -H, and **R₅** is -H, halogen, methyl, or trifluoromethyl.

[462] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₄** is -H or halogen (preferably **R₄** is -H), and **R₆** is -H, or halogen; more preferably **R₃** is -H, or methyl, and **R₄** and **R₆** are each H.

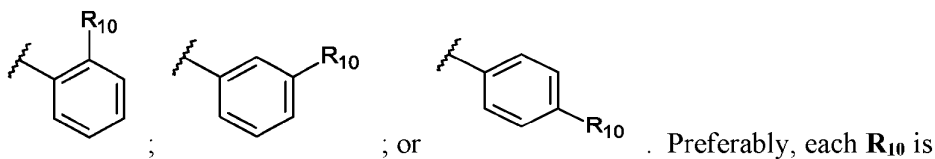
[463] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H, or halogen; more preferably **R₃** is -H, or methyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, and **R₆** is H.

[464] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₄** is -H or halogen (preferably **R₄** is -H), and **R₆** is -H, or halogen; more preferably **R₅** is -H, halogen, methyl, or trifluoromethyl, and **R₄** and **R₆** are each H.

[465] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₄** is -H or halogen (preferably **R₄** is -H), **R₅** is -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy, and **R₂** is a group of the formula:



more preferably **R₃** is -H, or methyl, **R₄** is -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, and **R₂** is a group of the formula:

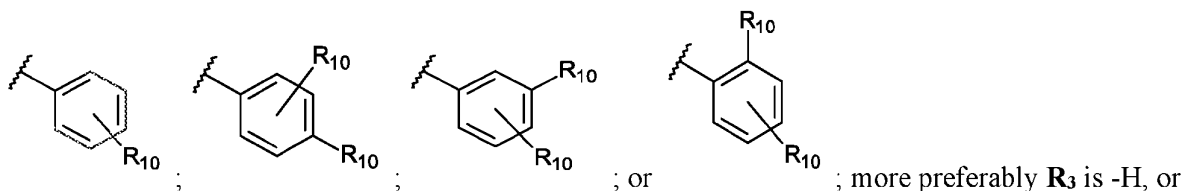


independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

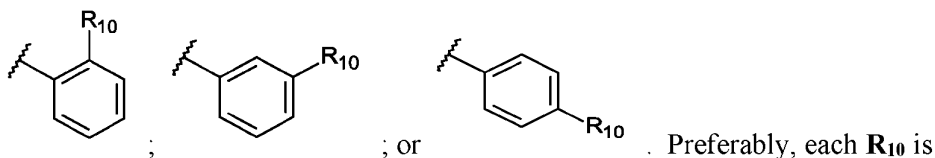
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haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with a $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_3$ alkoxy; the optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy, $-\text{NR}_{11}\text{R}_{11}$, $-\text{OH}$ or $-\text{CN}$.

[466] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is $-\text{H}$, $-\text{CN}$, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ haloalkyl (preferably R_3 is $-\text{H}$, $-\text{CN}$, or $\text{C}_1\text{-C}_3$ alkyl), R_4 is $-\text{H}$ or halogen (preferably R_4 is $-\text{H}$), R_6 is $-\text{H}$, or halogen, and R_2 is a group of the formula:



methyl, R_4 and R_6 are each $-\text{H}$, and R_2 is a group of the formula:

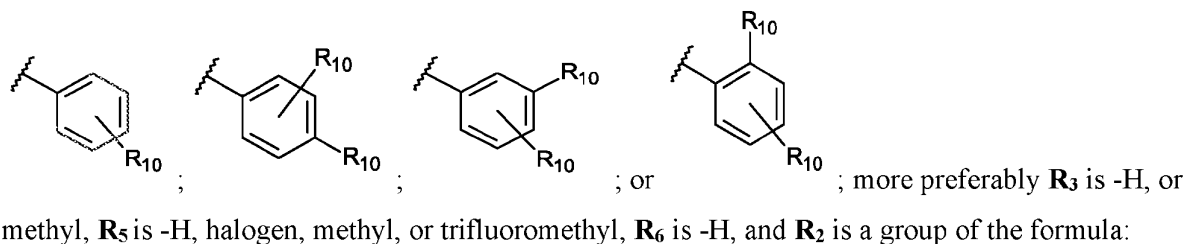
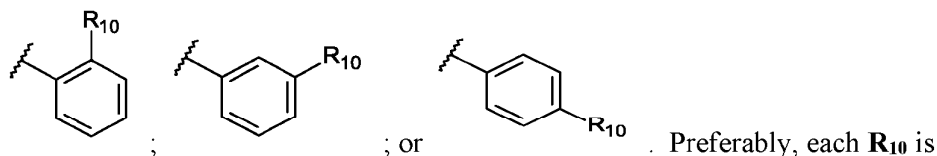


independently $-\text{H}$, $-\text{CN}$, halogen, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with a $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_3$ alkoxy; the optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen,

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C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

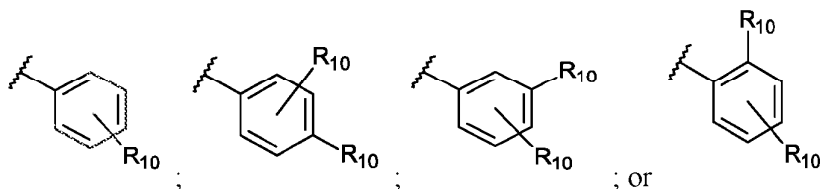
[467] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₅** is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, **R₆** is -H, or halogen, and **R₂** is a group of the formula:



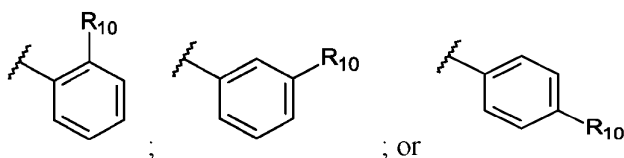
independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[468] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₄** is -H or halogen (preferably **R₄** is -H), **R₆** is -H, or halogen, and **R₂** is a group of the formula:

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; or ; more preferably R_5 is -H, halogen, methyl, or trifluoromethyl, R_4 is -H, R_6 is -H, or halogen, and R_2 is a group of the formula:

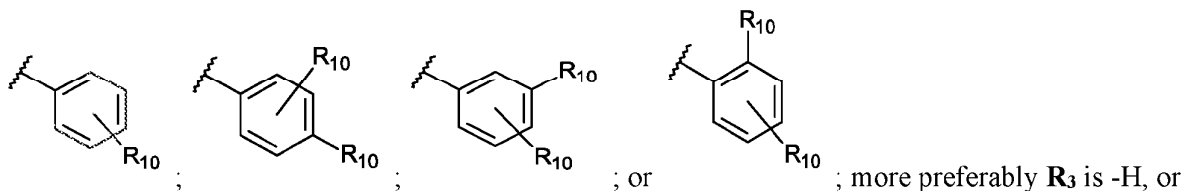


; or . Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

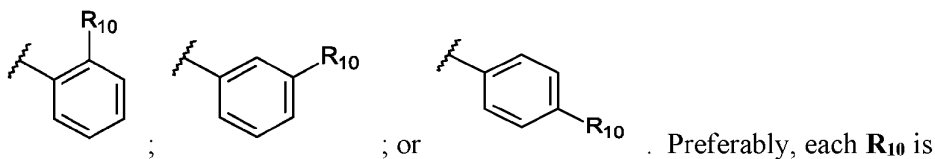
[469] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably R_3 is -H, -CN, or C₁-C₃ alkyl), R_4 is -H or halogen (preferably R_4 is -H), R_6 is -H, or halogen, and R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably R_3 is -H, or methyl, R_4 and R_6 are each -H, and R_5 is -H, halogen, methyl, or trifluoromethyl.

[470] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably R_3 is -H, -CN, or C₁-C₃ alkyl), R_4 is -H or halogen (preferably R_4 is -H), R_6 is -H, or halogen, R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and R_2 is a group of the formula:

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; more preferably R_3 is -H, or methyl, R_4 is -H, R_6 is -H, or halogen, R_5 is -H, halogen, methyl, or trifluoromethyl, and R_2 is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[471] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R is -H.

[472] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_7 is -CN, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; preferably R_7 is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably R_7 is -CN, methyl or trifluoromethyl.

[473] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_8 is -H.

[474] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_7 is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and R is -H. In yet a further compound of Formula (I), or

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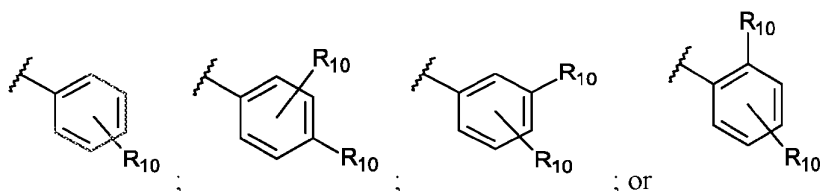
(II), or pharmaceutically acceptable salts thereof, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R** is -H.

[475] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₈ and **R** are each -H.

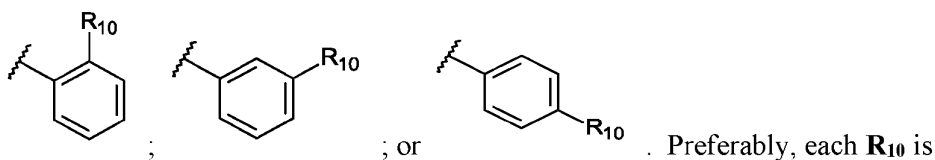
[476] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₈ is H. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₈ is H.

[477] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₈ and **R** are each -H. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₈ and **R** are each -H.

[478] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₈ is -H, **R** is -H, and **R**₂ is a group of the formula:



[479] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is C₁-C₃ alkyl (preferably methyl), **R**₈ is -H, **R** is -H, and **R**₂ is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH,

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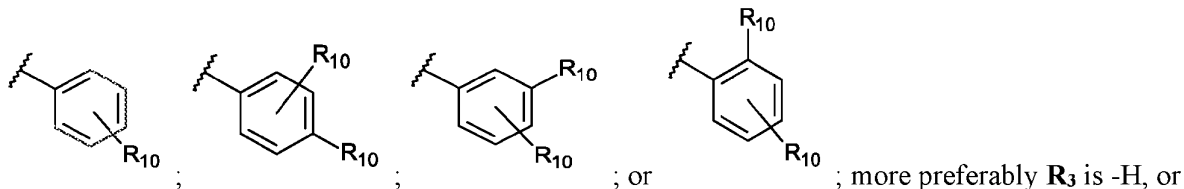
or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[480] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), **R**₇ is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₈ and **R** are each -H. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, or methyl, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₈ and **R** are each -H.

[481] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₄, **R**₈ and **R** are each -H. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₄, **R**₈ and **R** are each -H.

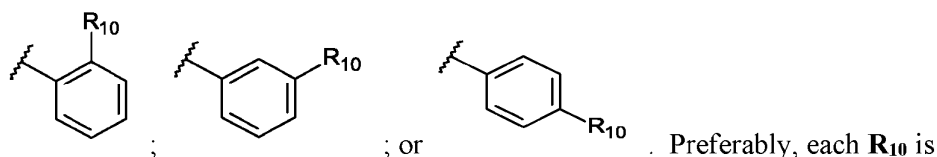
[482] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₈ and **R** are each -H. In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₇ is methyl, and **R**₈ and **R** are each -H.

[483] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), **R**₄ is -H or halogen (preferably **R**₄ is -H), **R**₆ is -H, or halogen, **R**₅ is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, **R**₇ is -CN, methyl or trifluoromethyl, **R**₈ is -H, **R** is -H, and **R**₂ is a group of the formula:



methyl, **R**₄ is -H, **R**₆ is -H, or halogen, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₇ is methyl, **R**₈ is -H, **R** is -H, and **R**₂ is a group of the formula:

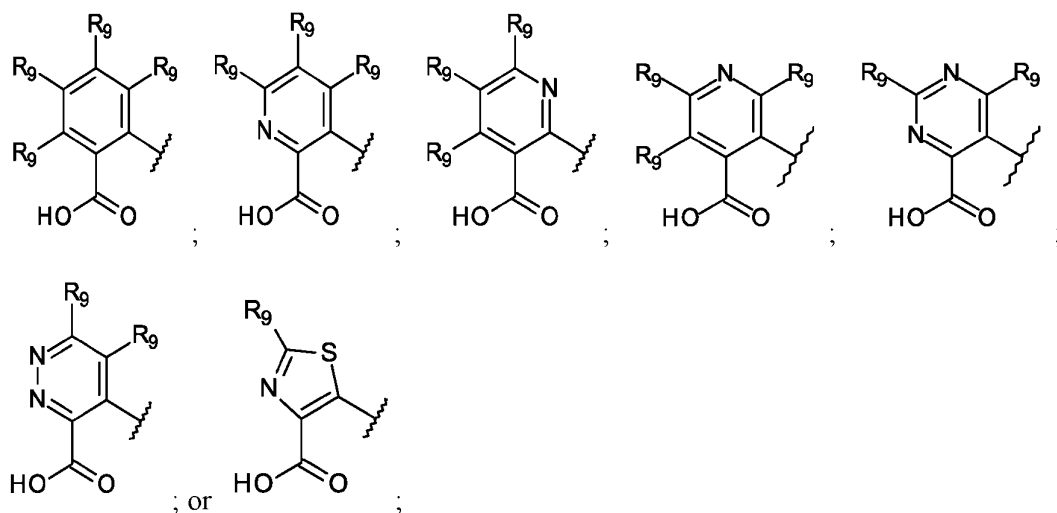
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independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[484] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

R₁ is a group of the formula:

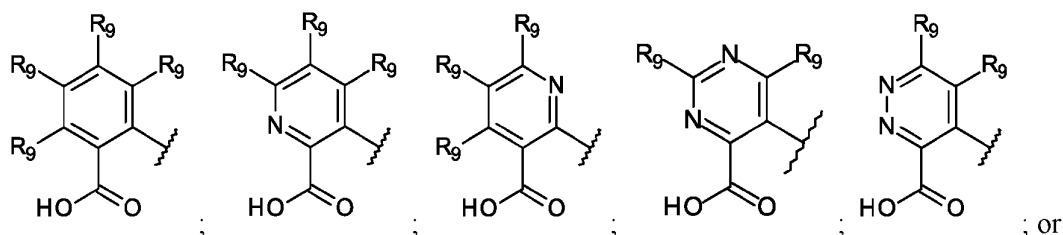
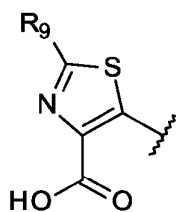


wherein each **R**₉ is independently -H, halogen, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, or C₃-C₅ cycloalkyl; preferably each **R**₉ is independently -H, halogen, -CN, methyl, trifluoromethyl,

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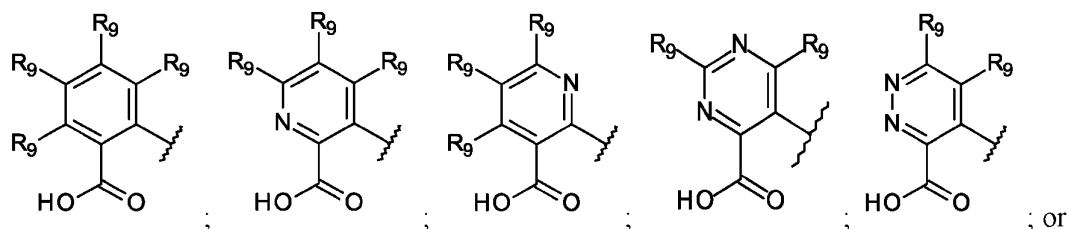
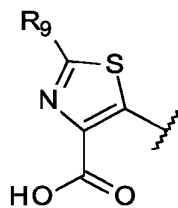
methoxy, or cyclopropyl.

[485] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl; preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, or C₃-C₅ cycloalkyl; more preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, methoxy, or cyclopropyl.

[486] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



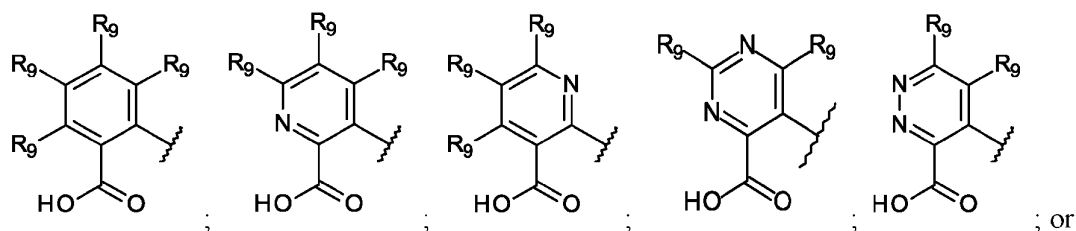
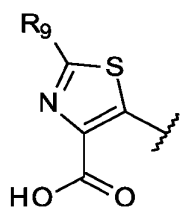
; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-

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C₅ cycloalkyl; preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[487] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

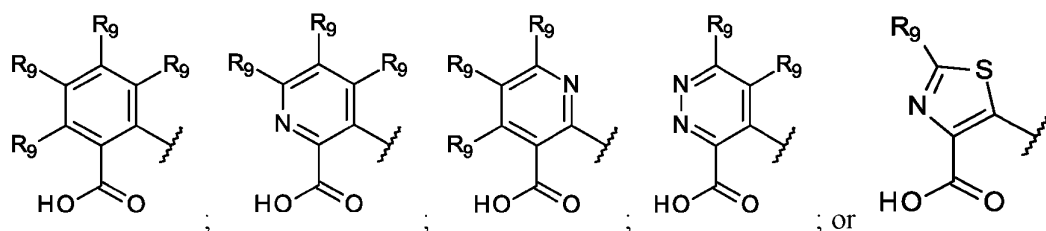
R₁ is a group of the formula:



; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably each **R₉** is independently -H, halogen, methyl or trifluoromethyl.

[488] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

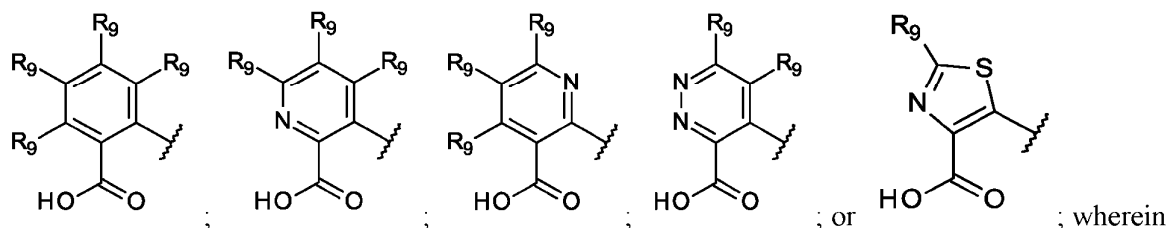
R₁ is a group of the formula:



[489] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

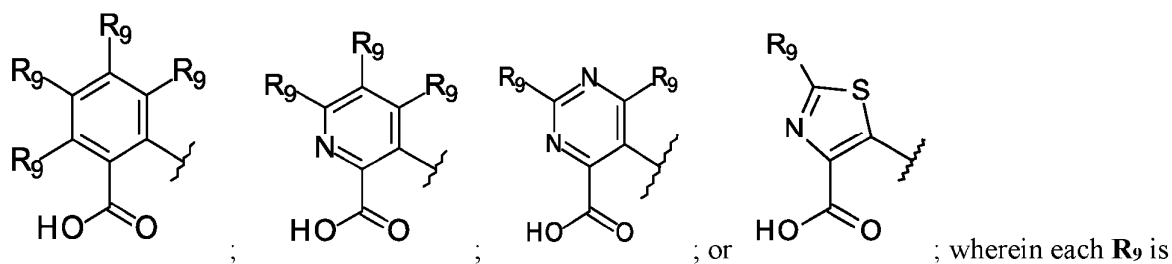
R₁ is a group of the formula:

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each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably each **R₉** is independently -H, halogen, methyl or trifluoromethyl.

[490] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

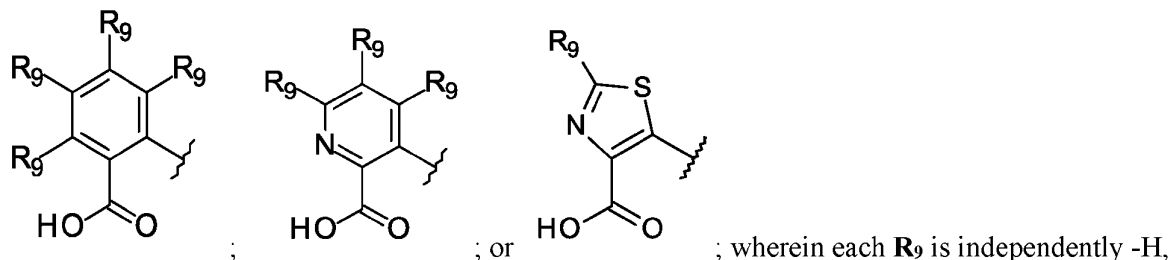


independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl.

Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl.

More preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[491] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

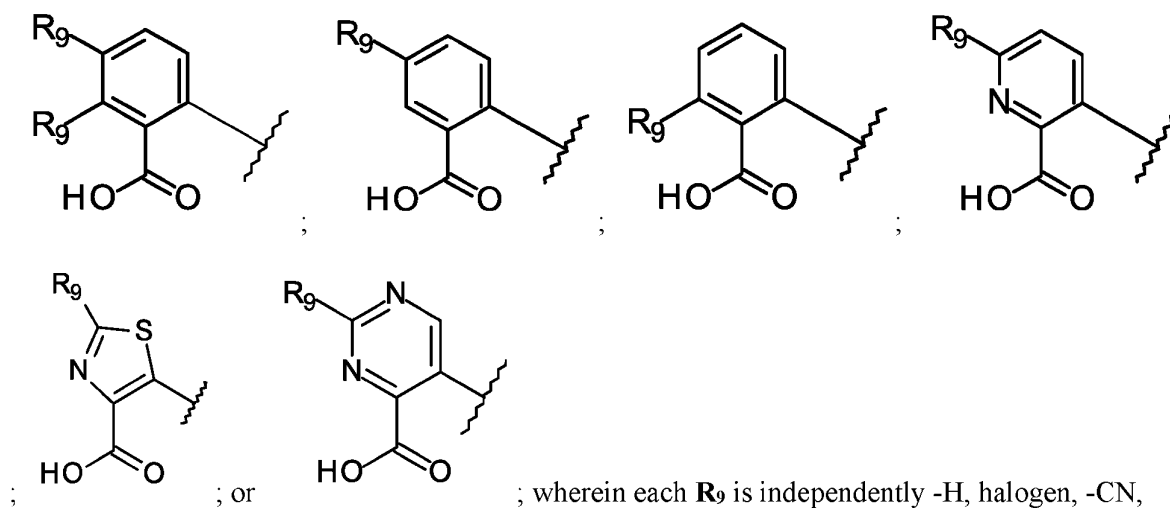


halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl. Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. More preferably each **R₉** is

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independently -H, halogen, methyl or trifluoromethyl.

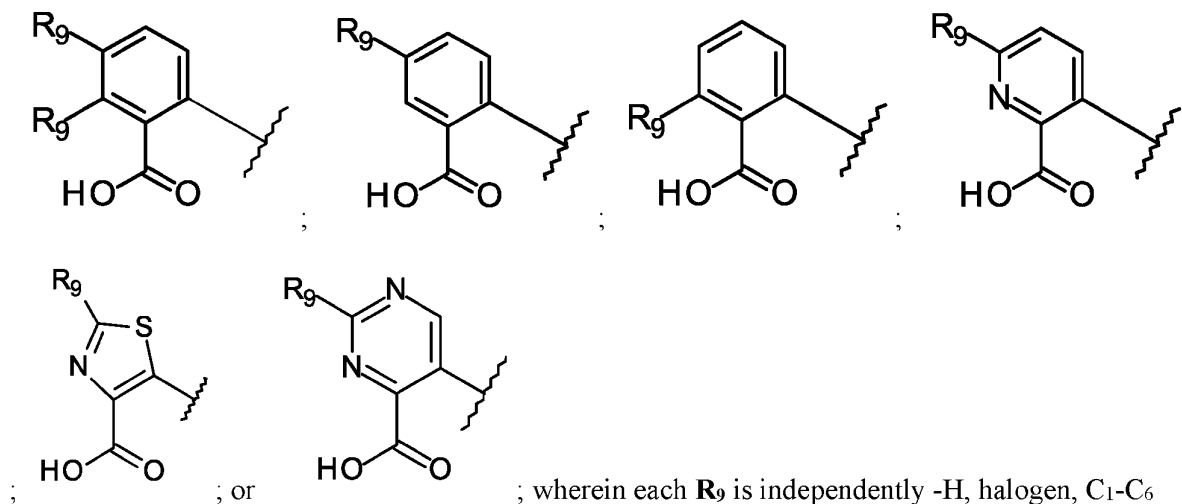
[492] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula



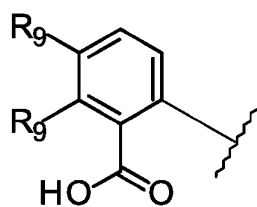
C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl; preferably each **R₉** is independently -H, halogen, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, or C₃-C₅ cycloalkyl; more preferably each **R₉** is independently -H, halogen, -CN, methyl, trifluoromethyl, methoxy, or cyclopropyl.

[493] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula

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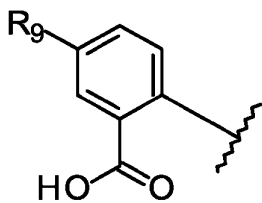
[494] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_1 is a group of the formula:



; wherein each R_9 is independently -H, halogen, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl or C₁-C₃ alkoxy. Preferably each R_9 is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. More preferably each R_9 is independently -H, halogen, methyl or trifluoromethyl.

[495] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_1 is a group of the formula:

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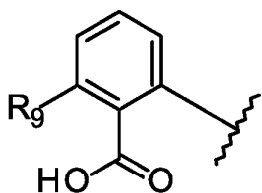


; wherein **R₉** is -H, halogen, -CN, C₁-C₃ haloalkyl, or C₁-C₃ alkoxy.

Preferably **R₉** is -H, halogen, or C₁-C₃ haloalkyl. More preferably **R₉** is -H, or trifluoromethyl.

[496] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

R₁ is a group of the formula:

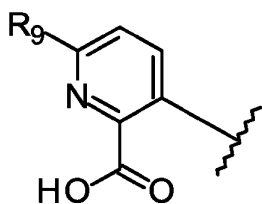


; wherein **R₉** is -H, halogen, -CN, C₁-C₃ haloalkyl, or C₁-C₃ alkoxy.

Preferably **R₉** is -H, halogen, or C₁-C₃ haloalkyl. More preferably **R₉** is -H, or halogen. Even more preferably, **R₉** is -H, or fluoro.

[497] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

R₁ is a group of the formula:



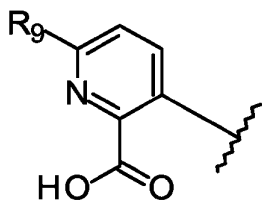
; wherein **R₉** is -H, halogen, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃

alkoxy, or C₃-C₅ cycloalkyl. Preferably **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. More preferably **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[498] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

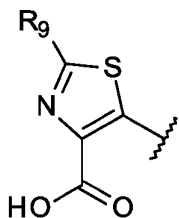
R₁ is a group of the formula:

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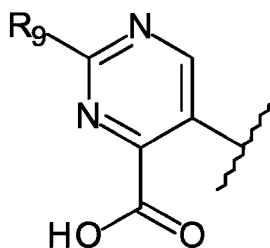
; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl. Preferably **R₉** is independently halogen or trifluoromethyl. More preferably **R₉** is chloro or trifluoromethyl.

[499] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl or C₁-C₆ alkoxy. Preferably **R₉** is -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl. More preferably **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl.

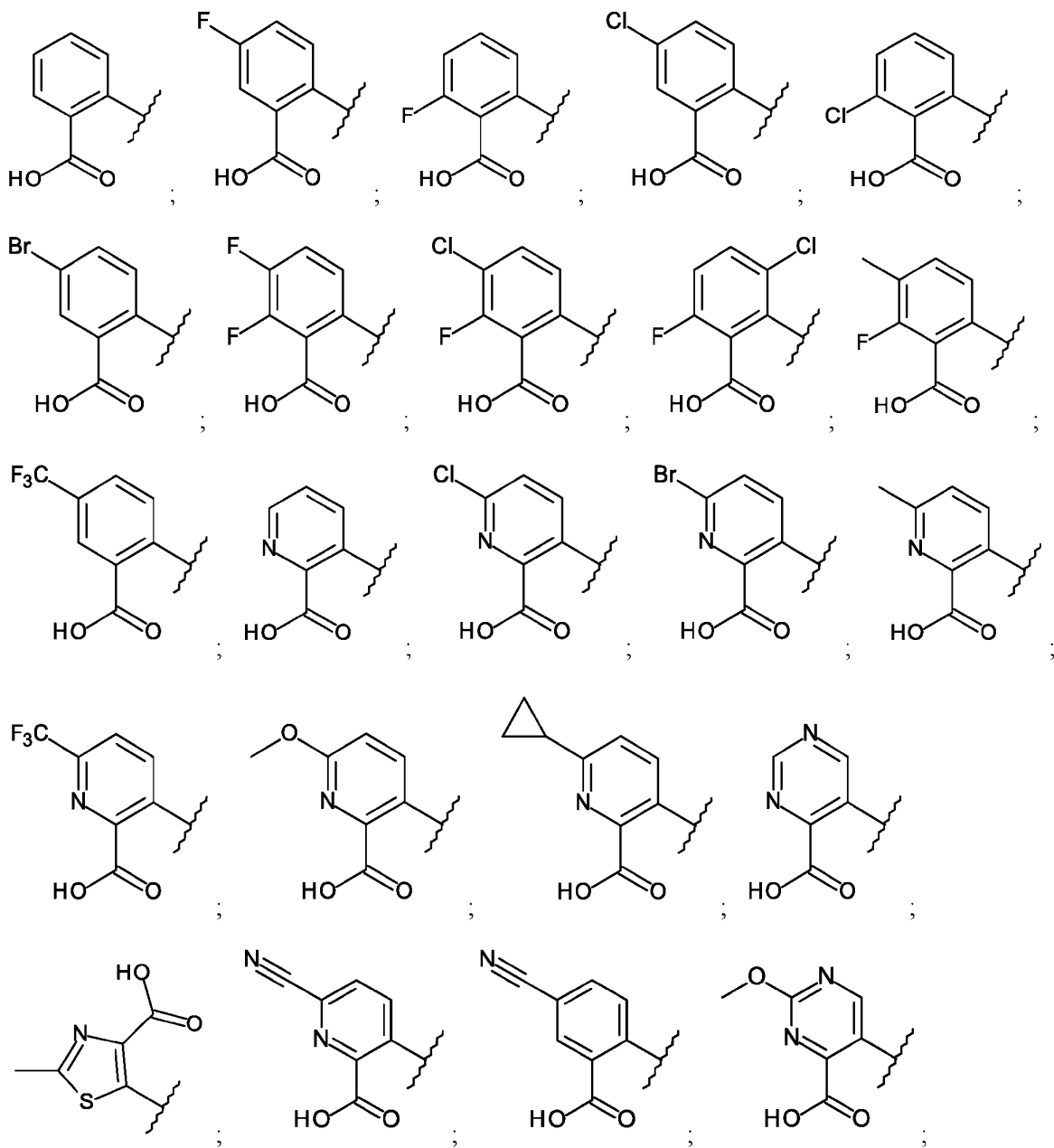
[500] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



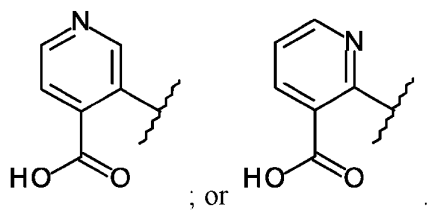
; wherein **R₉** is -H, halogen, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, or C₃-C₅ cycloalkyl. Preferably **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. More preferably **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[501] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

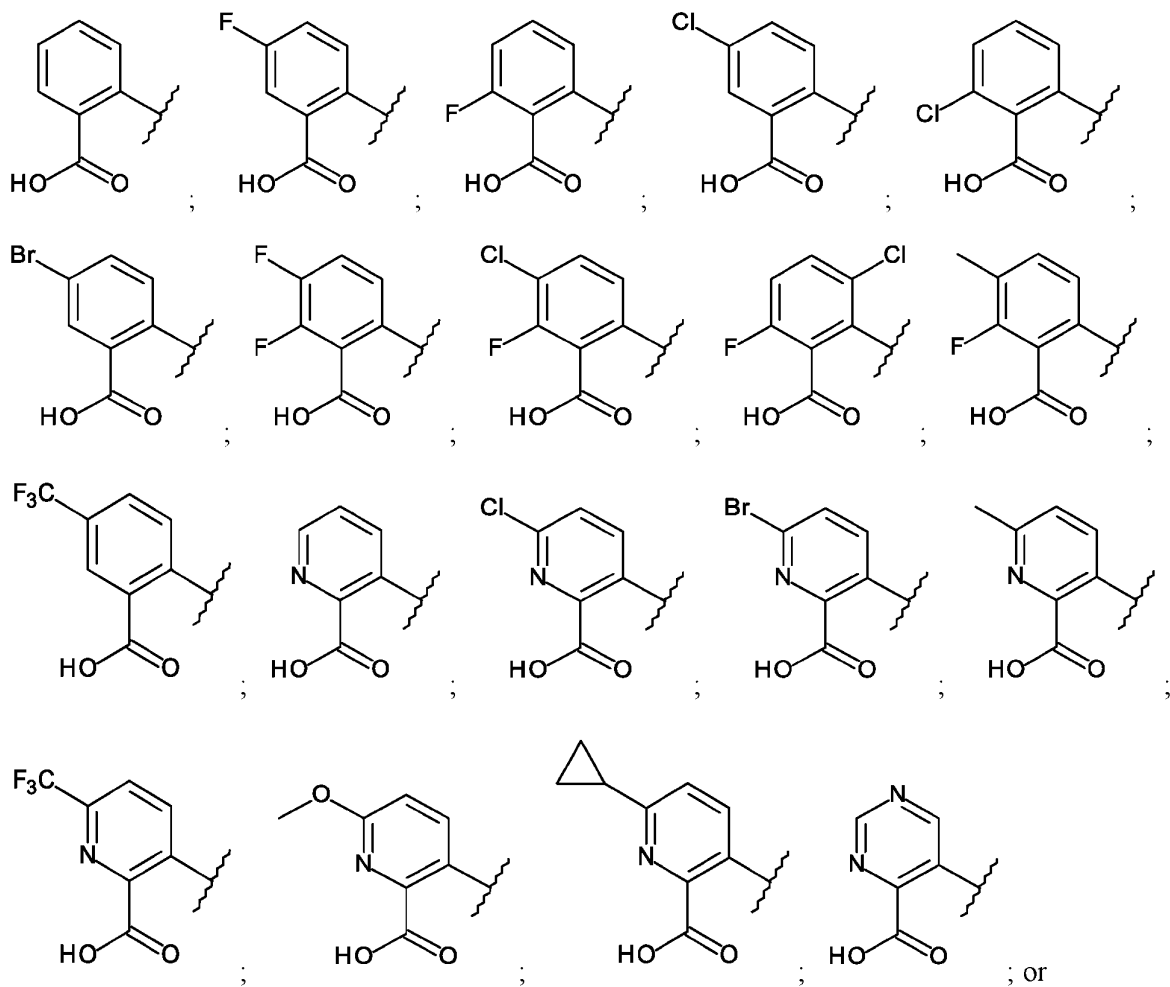
- 190 -



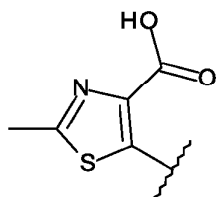
- 191 -



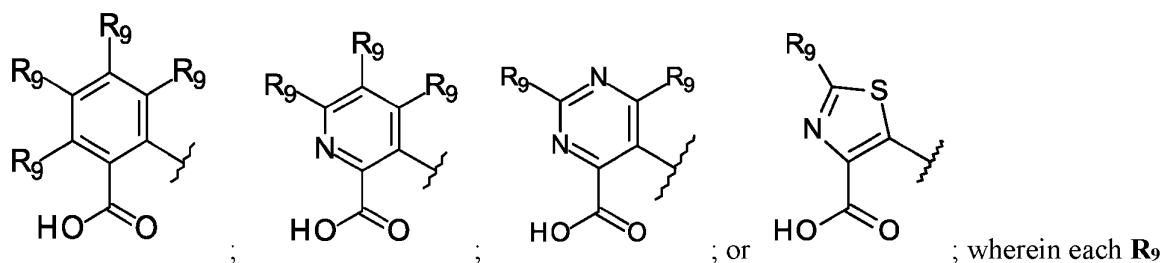
[502] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_1 is a group of the formula:



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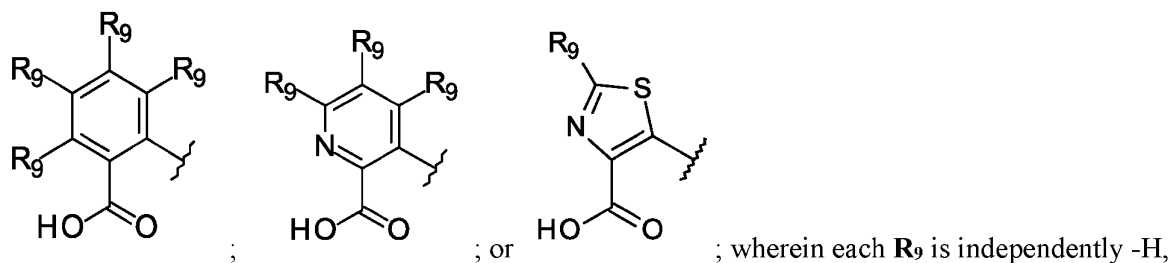


[503] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R₄** is -H, or halogen, **R₆** is -H, or halogen, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₁** is a group of the formula:



wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. More preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably **R₃** is -H, methyl, or trifluoromethyl, **R₄** is -H, or halogen, **R₆** is -H, or halogen, **R₅** is -H, halogen, methyl, or trifluoromethyl, and each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[504] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, or C₁-C₃ alkyl, **R₄** is -H, **R₆** is -H, or halogen, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₁** is a group of the formula:

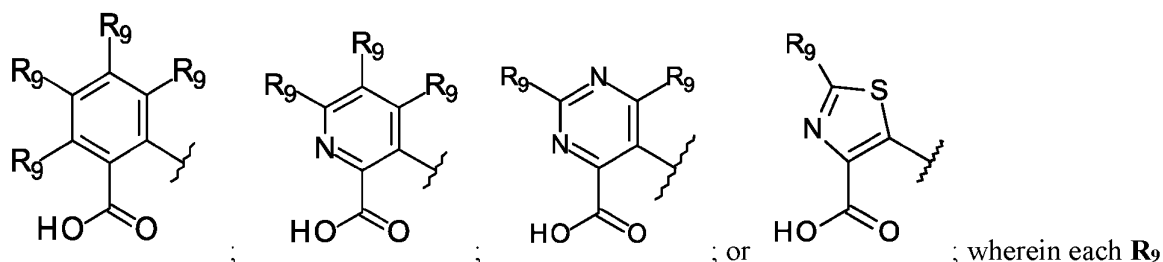


wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. Preferably **R₃** is -H, or methyl, **R₄** is -H, **R₆** is -H, or halogen, **R₅** is -H, halogen, methyl, or trifluoromethyl, and each **R₉** is independently -H, halogen,

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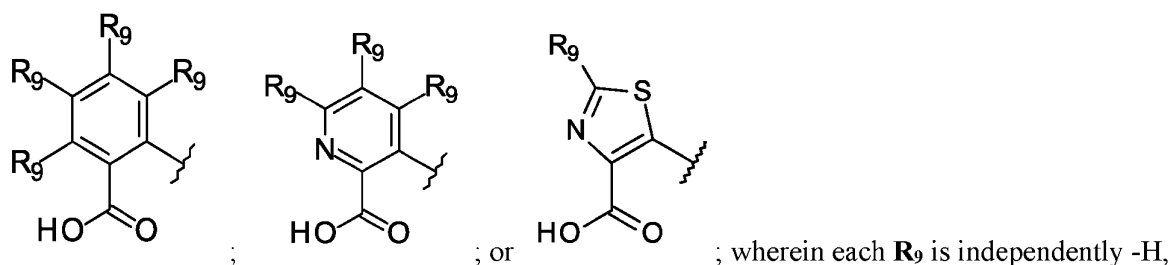
methyl, or trifluoromethyl.

[505] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, methyl or trifluoromethyl, **R**₈ and **R** are each -H, and **R**₁ is a group of the formula:



is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl; more preferably **R**₇ is methyl, **R**₈ and **R** are each -H, and each **R**₉ is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

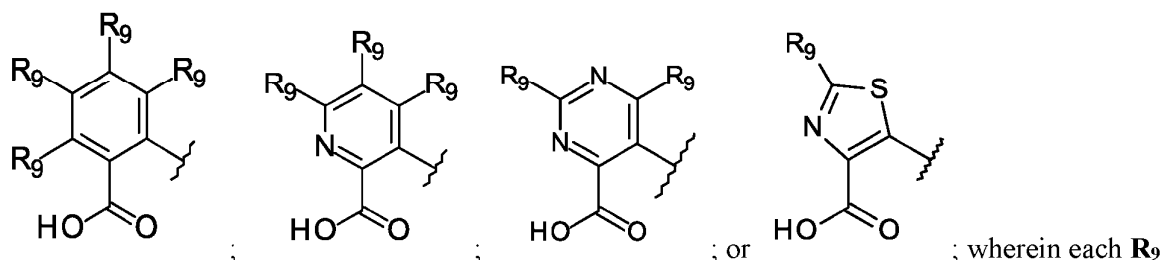
[506] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₇ is -CN, methyl or trifluoromethyl, **R**₈ and **R** are each -H, and **R**₁ is a group of the formula:



halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R**₇ is methyl, **R**₈ and **R** are each -H, and each **R**₉ is independently -H, halogen, methyl, or trifluoromethyl.

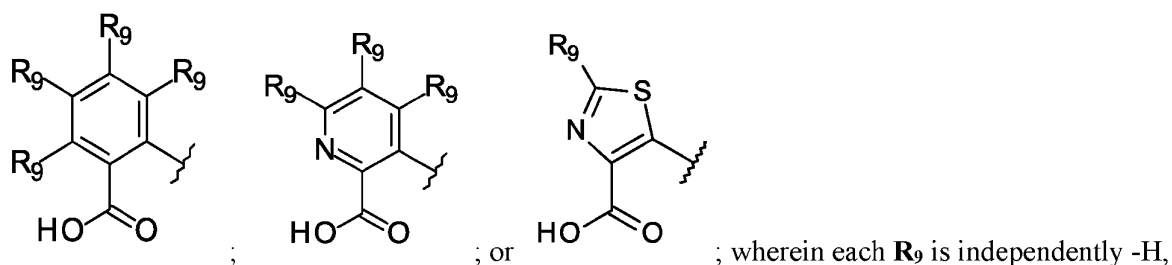
[507] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R**₄ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H, or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:

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wherein each R_9 is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl; more preferably R_3 is -H, methyl, or trifluoromethyl, R_4 is -H, or halogen, R_6 is -H, or halogen, R_8 and R are each -H, R_5 is -H, halogen, methyl, or trifluoromethyl, R_7 is methyl, and each R_9 is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

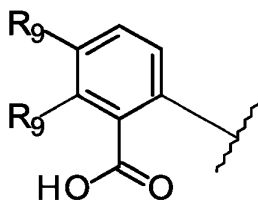
[508] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is -H, -CN, or C₁-C₃ alkyl, R_4 , R_8 and R are each -H, R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, R_6 is -H, or halogen, R_7 is -CN, methyl or trifluoromethyl, and R_1 is a group of the formula:



wherein each R_9 is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably R_3 is -H, or methyl, R_4 , R_6 , R_8 and R are each -H, R_5 is -H, halogen, methyl, or trifluoromethyl, R_7 is methyl, and each R_9 is independently -H, halogen, methyl, or trifluoromethyl.

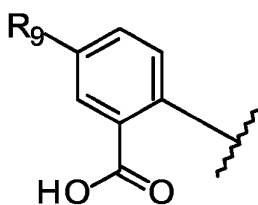
[509] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_3 is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, R_4 is -H, or halogen, R_8 and R are each -H, R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, R_6 is -H, or halogen, R_7 is -CN, methyl or trifluoromethyl, and R_1 is a group of the formula:

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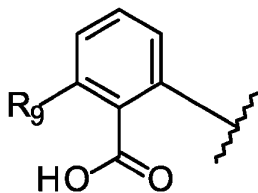
; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably **R₃** is -H, methyl, or trifluoromethyl, **R₄** is -H, or halogen, **R₆** is -H, or halogen, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₇** is methyl, and each **R₉** is independently -H, halogen, methyl or trifluoromethyl.

[510] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, or C₁-C₃ alkyl, **R₄**, **R₈** and **R** are each -H, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H, or halogen, **R₇** is -CN, methyl or trifluoromethyl, and **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl; preferably **R₃** is -H, or methyl, **R₄**, **R₆**, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₇** is methyl, and **R₉** is -H, or trifluoromethyl.

[511] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, or C₁-C₃ alkyl, **R₄**, **R₈** and **R** are each -H, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H, or halogen, **R₇** is -CN, methyl or trifluoromethyl, and **R₁** is a group of the formula:

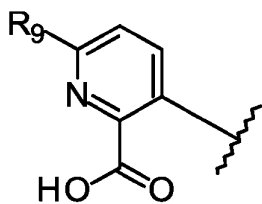


; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl; preferably **R₃** is -H, or

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methyl, **R**₄, **R**₆, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₇ is methyl, and **R**₉ is -H, or halogen, more preferably **R**₉ is -H, or fluoro.

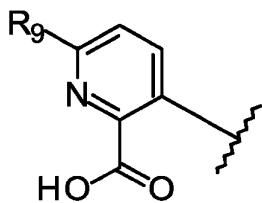
[512] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R**₄ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H, or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:



; wherein **R**₉ is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅

cycloalkyl; preferably **R**₃ is -H, methyl, or trifluoromethyl, **R**₄ is -H, or halogen, **R**₆ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₇ is methyl, and **R**₉ is -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[513] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, or C₁-C₃ alkyl, **R**₄, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H, or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:



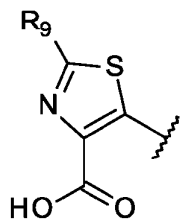
; wherein **R**₉ is -H, halogen, or C₁-C₃ haloalkyl; preferably **R**₃ is -H, or

methyl, **R**₄, **R**₆, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₇ is methyl, and **R**₉ is independently halogen or trifluoromethyl.

[514] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₃ is -H, -CN, or C₁-C₃ alkyl, **R**₄, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H, or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the

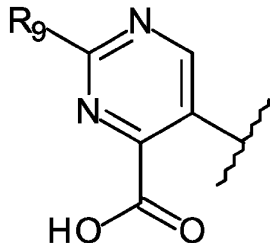
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formula:



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably **R₃** is -H, or methyl, **R₄**, **R₆**, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₇** is methyl, and **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl.

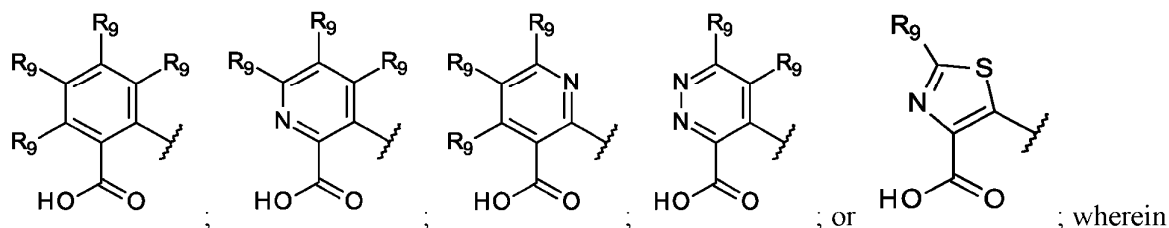
[515] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R₄** is -H, or halogen, **R₈** and **R** are each -H, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H, or halogen, **R₇** is -CN, methyl or trifluoromethyl, and **R₁** is a group of the formula:



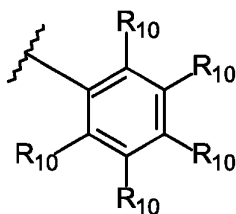
; wherein **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl; preferably **R₃** is -H, methyl, or trifluoromethyl, **R₄** is -H, or halogen, **R₆** is -H, or halogen, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₇** is methyl, and **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[516] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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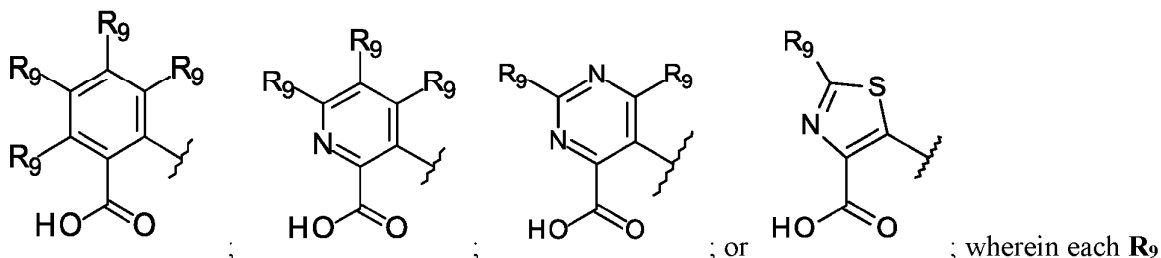
each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:



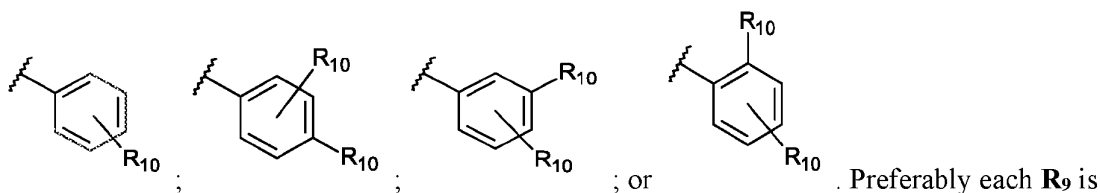
wherein each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[517] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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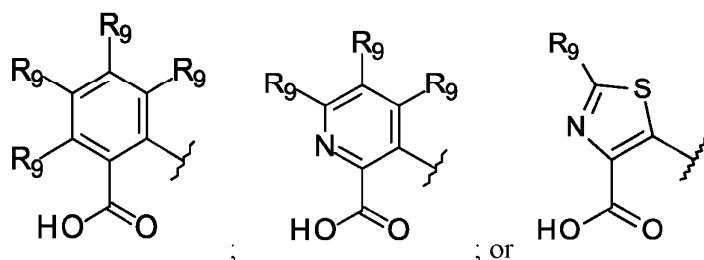
is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:



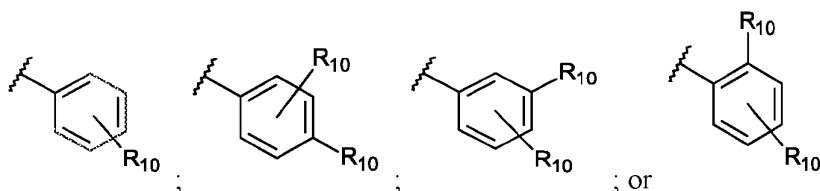
independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Most preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[518] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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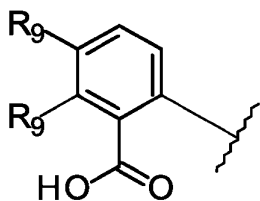
; or ; wherein each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:



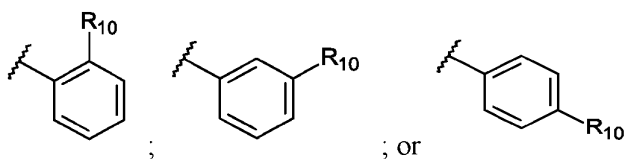
; or . Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. Most preferably each **R₉** is independently -H, halogen, methyl, or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[519] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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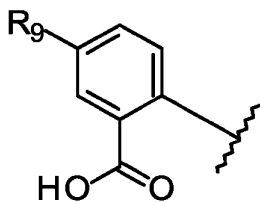


; wherein each **R**₉ is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R**₂ is a group of the formula:



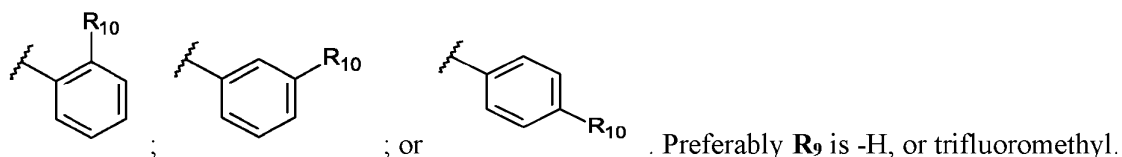
Preferably each **R**₉ is independently -H, halogen, methyl or trifluoromethyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[520] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



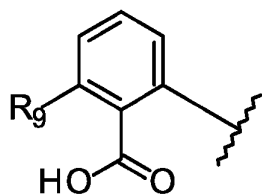
; wherein **R**₉ is -H, halogen, or C₁-C₃ haloalkyl, and **R**₂ is a group of the formula:

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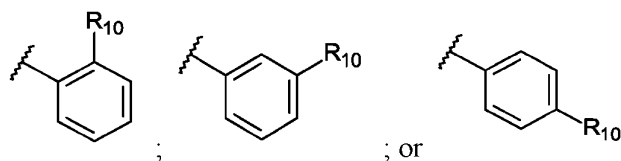
. Preferably **R₉** is -H, or trifluoromethyl.

Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[521] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl, and **R₂** is a group of the

formula:

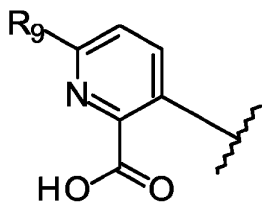
. Preferably **R₉** is -H, or halogen. Preferably,

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an

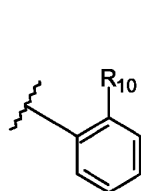
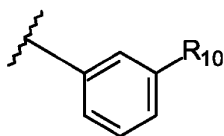
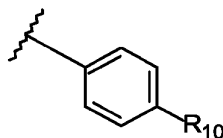
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optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[522] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, and **R**₂ is a group of the formula:



;

; or

; preferably **R**₉ is -H,

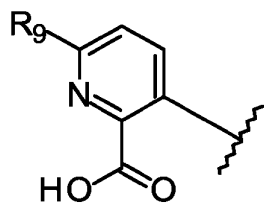
halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen,

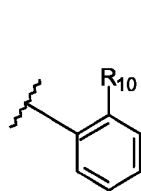
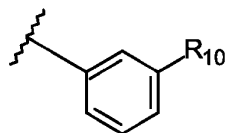
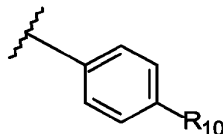
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C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[523] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is halogen, or C₁-C₃ haloalkyl, and **R**₂ is a group of the formula:



;

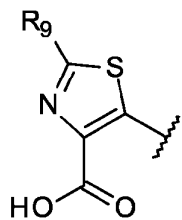
; or

; preferably **R**₉ is halogen or

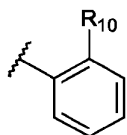
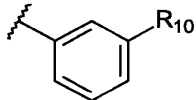
trifluoromethyl. More preferably **R**₉ is chloro or trifluoromethyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[524] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:

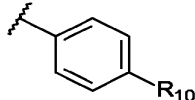
- 205 -



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:

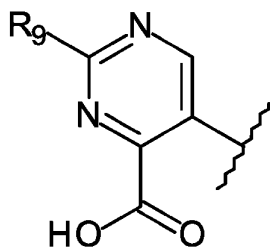


; or

. Preferably, each **R₁₀** is

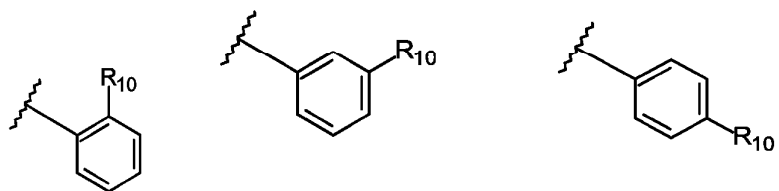
independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[525] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:

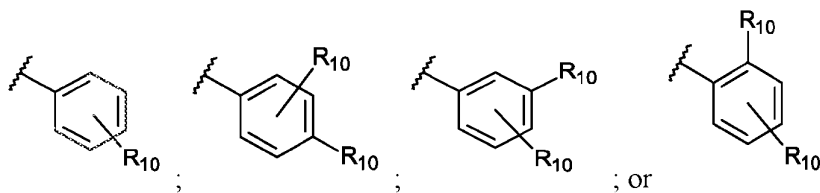
- 206 -



; or ; preferably R_9 is -H,

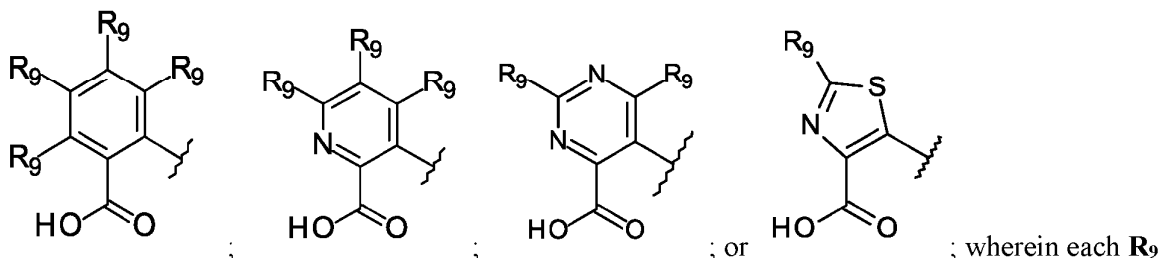
halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[526] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, R_2 is a group of the formula:



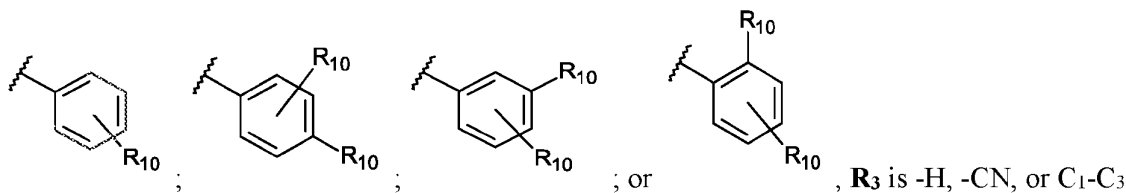
; or , R_3 is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, R_4 is -H, or halogen, R_6 is -H, or halogen, R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and R_1 is a group of the formula:

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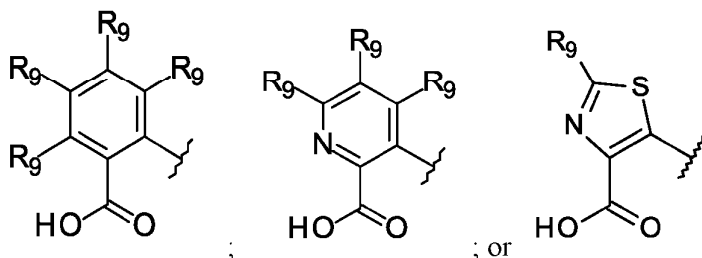
wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Preferably **R₃** is -H, methyl, or trifluoromethyl, **R₄** is -H, or halogen, **R₆** is -H, or halogen, **R₅** is -H, halogen, methyl, or trifluoromethyl, and each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[527] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



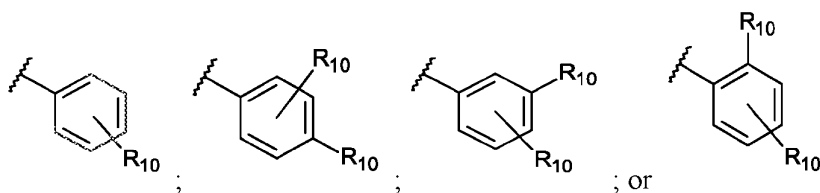
, **R₃** is -H, -CN, or C₁-C₃ alkyl, **R₄** is -H, **R₆** is -H, or halogen, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₁** is a group of the formula:

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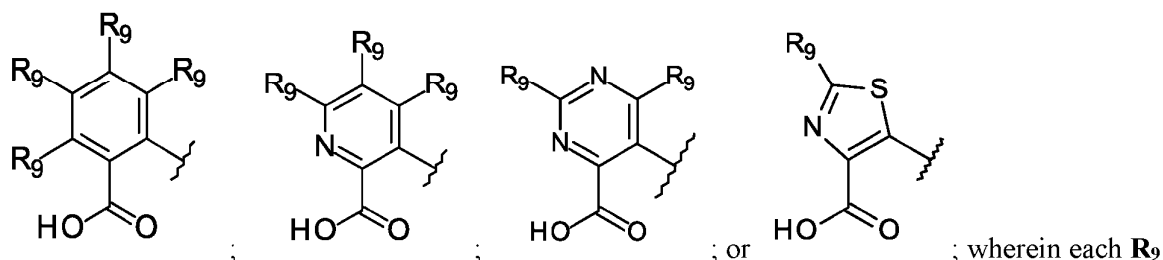
; or ; wherein each **R₉** is independently -H, halogen, or C₁-C₃ haloalkyl. Preferably **R₃** is -H, or methyl, **R₄** and **R₆** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, and each **R₉** is independently -H, halogen, methyl, or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[528] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



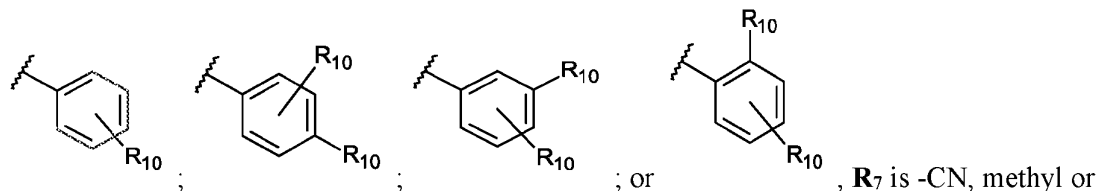
; or , **R₇** is -CN, methyl or trifluoromethyl, **R₈** and **R** are each -H, and **R₁** is a group of the formula:

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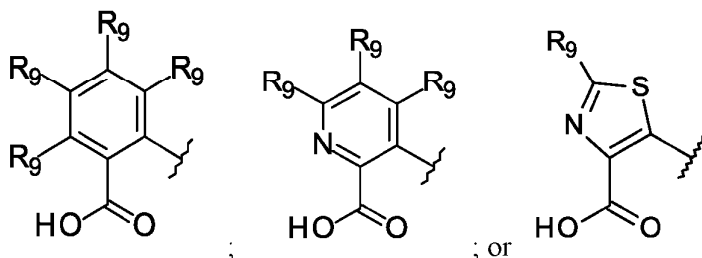
is independently -H, halogen, methyl, C₁-C₃ haloalkyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[529] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



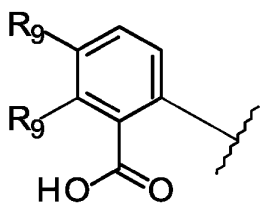
trifluoromethyl, **R₈** and **R** are each -H, and **R₁** is a group of the formula:

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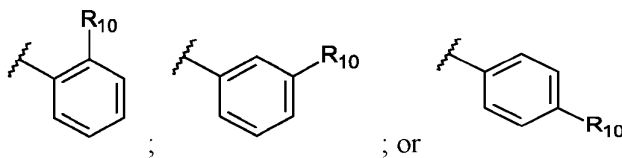
; wherein each **R₉** is independently -H, halogen, methyl, or C₁-C₃ haloalkyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[530] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, methyl or trifluoromethyl,

R₂ is a group of the formula:

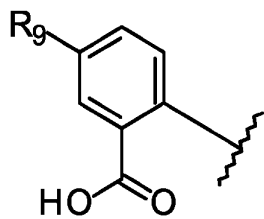


, **R₇** is C₁-C₃ alkyl (preferably methyl), and

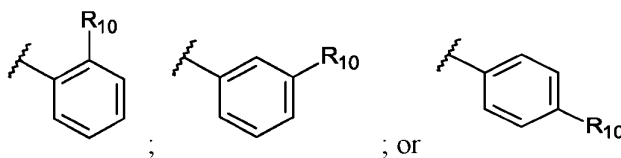
- 211 -

R₈ and **R** are each -H. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[531] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or trifluoromethyl, (preferably **R₉** is -H, or trifluoromethyl), **R₂** is a group of the formula:



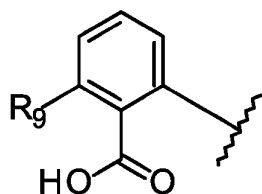
; or , **R₇** is C₁-C₃ alkyl (preferably methyl), and

R₈ and **R** are each -H. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is

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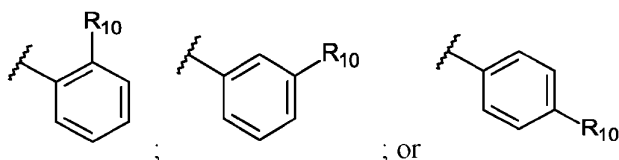
optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[532] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is -H, halogen, or C₁-C₃ haloalkyl (preferably **R**₉ is -H, or

halogen), **R**₂ is a group of the formula:



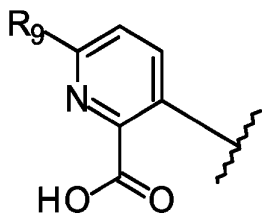
; or

, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₈

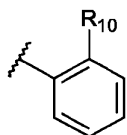
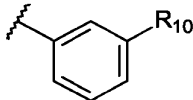
and **R** are each -H. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[533] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:

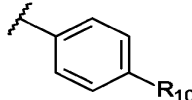
- 213 -



; wherein **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl, **R₂** is a group of the formula:

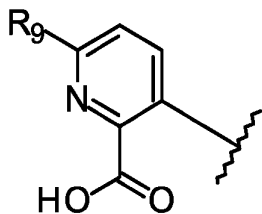


; or



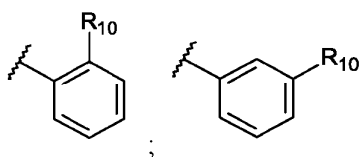
, **R₇** is C₁-C₃ alkyl (preferably methyl), and **R₈** and **R** are each -H. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[534] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

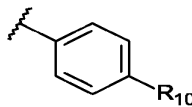


; wherein **R₉** is -H, halogen, or trifluoromethyl (preferably **R₉** is halogen or trifluoromethyl), **R₂** is a group of the formula:

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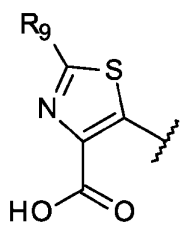


; or

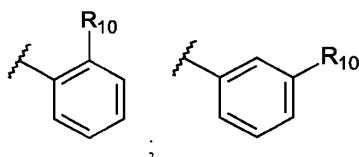
, **R**₇ is C₁-C₃ alkyl (preferably methyl), and

R₈ and **R** are each -H. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂**R**₁₁, -CONR₁₁**R**₁₁, -NR₁₁**R**₁₁, -NR₁₁-CO₂**R**₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁**R**₁₁, -OH or -CN.

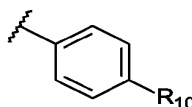
[535] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₂ is a group of the formula:



; or

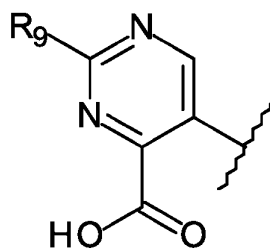
, **R**₇ is C₁-C₃ alkyl (preferably methyl), and

R₈ and **R** are each -H. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂**R**₁₁, -CONR₁₁**R**₁₁, -NR₁₁**R**₁₁, -NR₁₁-CO₂**R**₁₁, an optionally

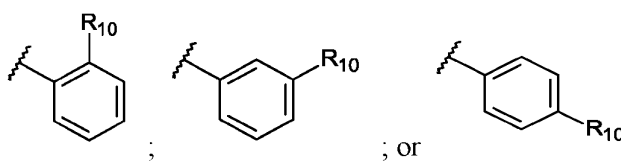
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substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[536] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, **R**₂ is a group of the formula:

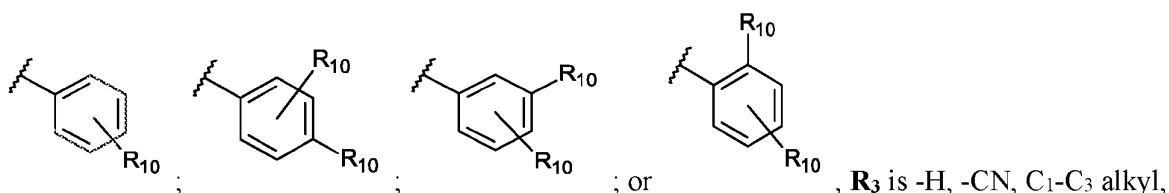


, **R**₇ is C₁-C₃ alkyl (preferably methyl), and **R**₈ and **R** are each -H. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl,

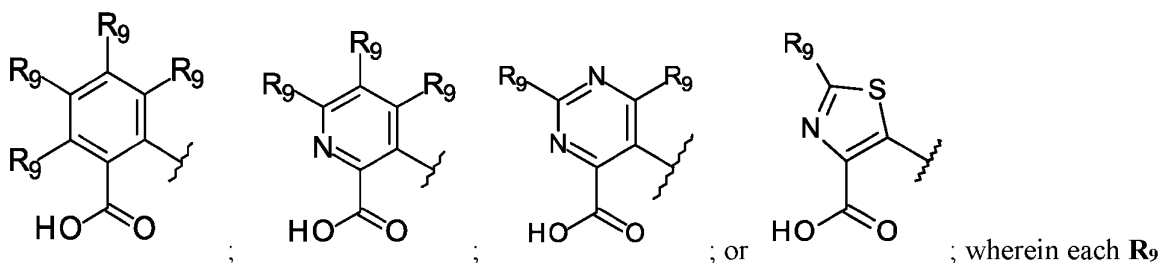
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phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[537] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



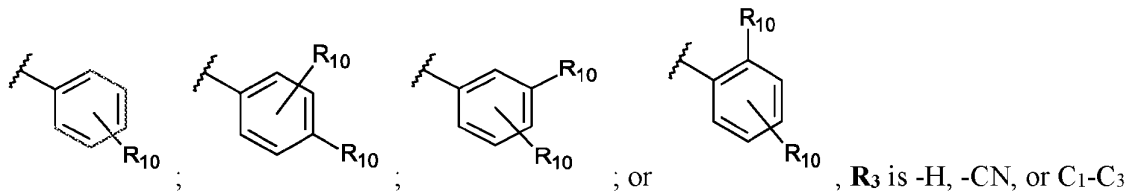
, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R**₄ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is H, or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:



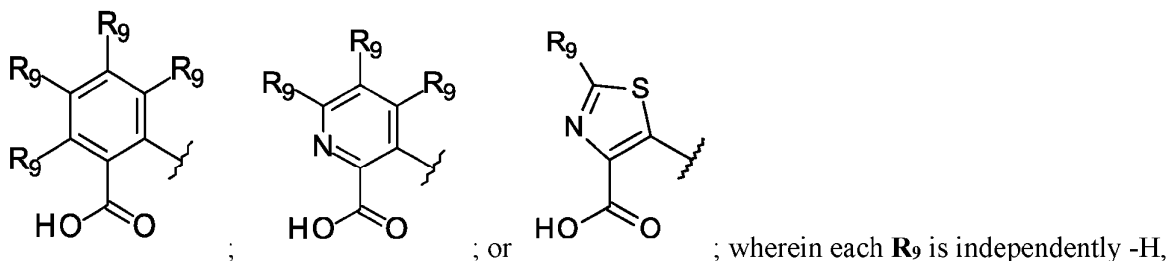
is independently -H, halogen, methyl, C₁-C₃ haloalkyl, or cyclopropyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

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[538] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



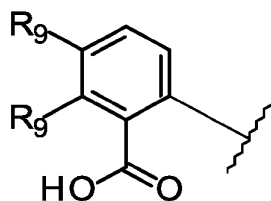
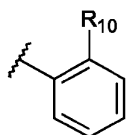
alkyl, **R₄**, **R₈** and **R** are each -H, **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H or halogen, **R₇** is -CN, methyl or trifluoromethyl, and **R₁** is a group of the formula:



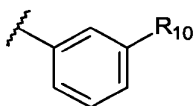
halogen, methyl, or C₁-C₃ haloalkyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[539] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

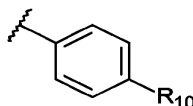
- 218 -

; wherein each **R₉** is independently -H, halogen, methyl or trifluoromethyl,**R₂** is a group of the formula:

;



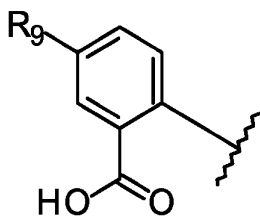
; or

, **R₃** is -H, methyl, or trifluoromethyl, **R₄**

is -H, or halogen, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl or trifluoromethyl, **R₆** is -H, or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

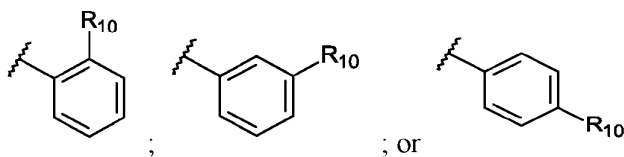
haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[540] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof,

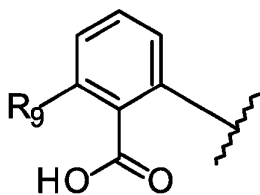
R₁ is a group of the formula:; wherein **R₉** is -H, halogen, or trifluoromethyl, (preferably **R₉** is -H, or

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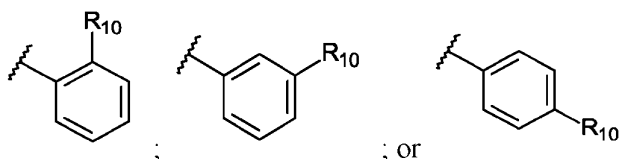
trifluoromethyl), **R**₂ is a group of the formula:



, **R**₃ is -H, or methyl, **R**₄, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₆ is -H or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl). Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN. [541] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



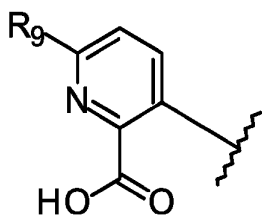
; wherein **R**₉ is -H, halogen, or C₁-C₃ haloalkyl (preferably **R**₉ is -H, or halogen), **R**₂ is a group of the formula:



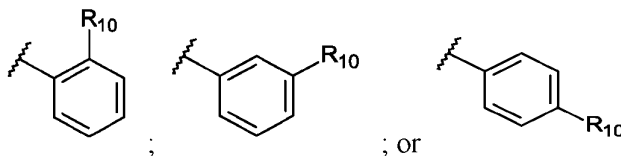
, **R**₃ is -H, or methyl, **R**₄, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₆ is -H or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl). Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆

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alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN. [542] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



; wherein **R**₉ is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl, **R**₂ is a group of the formula:

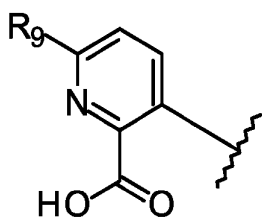


; or **R**₃ is -H, methyl, or trifluoromethyl, **R**₄ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl or trifluoromethyl, **R**₆ is -H, or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl). Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH,

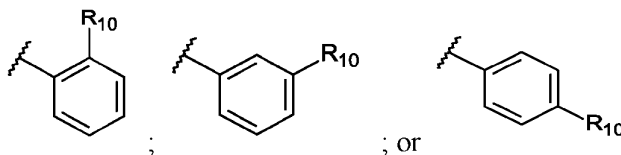
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or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[543] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



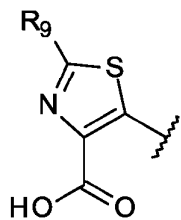
; wherein **R**₉ is -H, halogen, or trifluoromethyl, (preferably **R**₉ is halogen or trifluoromethyl), **R**₂ is a group of the formula:



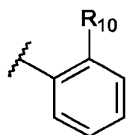
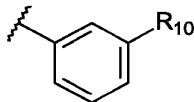
; or **R**₃ is -H, or methyl, **R**₄, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₆ is -H or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl). Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[544] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:

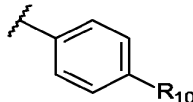
- 222 -



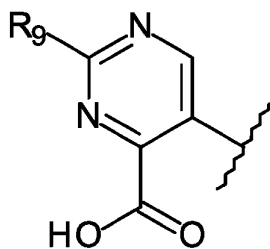
; wherein **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₂** is a group of the formula:



; or



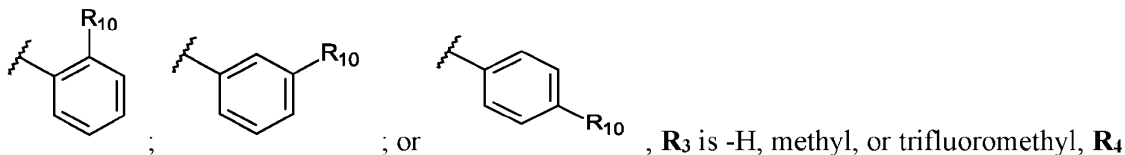
, **R₃** is -H, or methyl, **R₄**, **R₈** and **R** are each -H, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN. [545] In yet a further compound of Formula (I), or (II), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl, **R₂** is

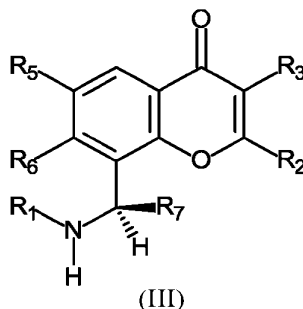
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a group of the formula:



, **R**₃ is -H, methyl, or trifluoromethyl, **R**₄ is -H, or halogen, **R**₈ and **R** are each -H, **R**₅ is -H, halogen, methyl or trifluoromethyl, **R**₆ is -H, or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl). Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

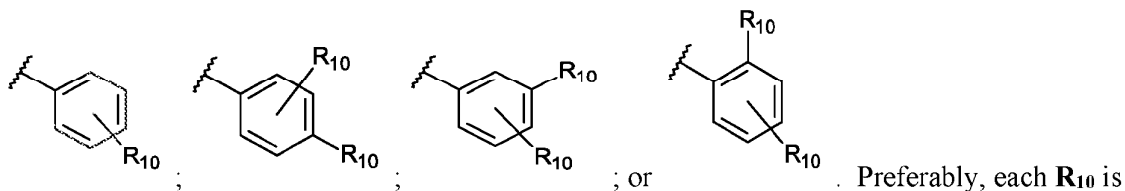
[546] In a further aspect, compounds of Formula (I) or (II) have Formula (III), or pharmaceutically acceptable salts thereof:



wherein **R**₁, **R**₂, **R**₃, **R**₅, **R**₆, and **R**₇ are as defined in the Summary for Formula (I) above.

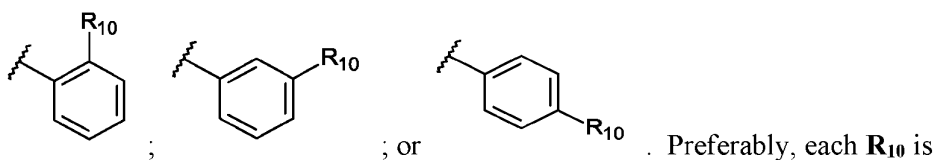
[547] In a compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:

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independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[548] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

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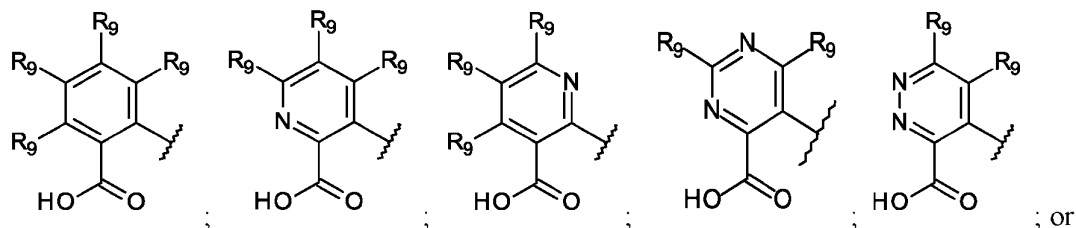
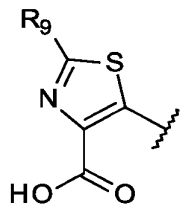
[549] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₃** is -H, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl; preferably **R₃** is -H, -CN, or C₁-C₃ alkyl; most preferably **R₃** is -H, or methyl.

[550] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₅** is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; preferably **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R₅** is -H, halogen, methyl, or trifluoromethyl.

[551] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₆** is -H or halogen; preferably **R₆** is -H.

[552] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₇** is -CN, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; preferably **R₇** is -CN, C₁-C₃ alkyl or C₁-C₃ haloalkyl; more preferably **R₇** is -CN, methyl or trifluoromethyl.

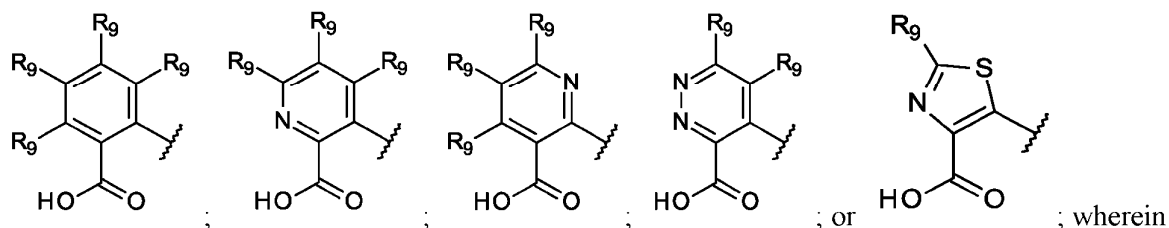
[553] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl; preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

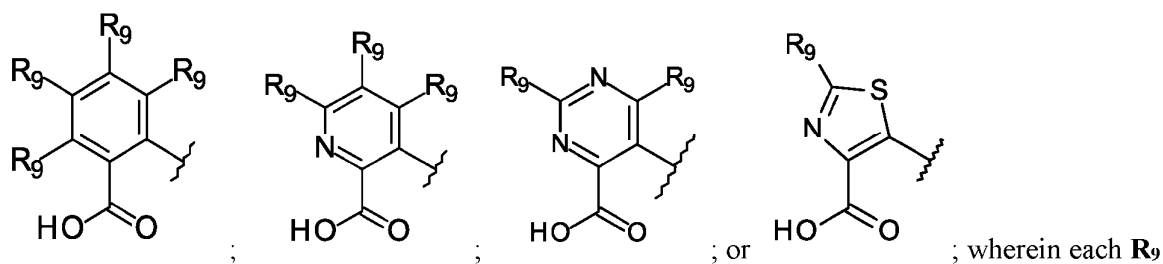
[554] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl; preferably each **R₉** is independently -H, halogen, methyl, or trifluoromethyl.

[555] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

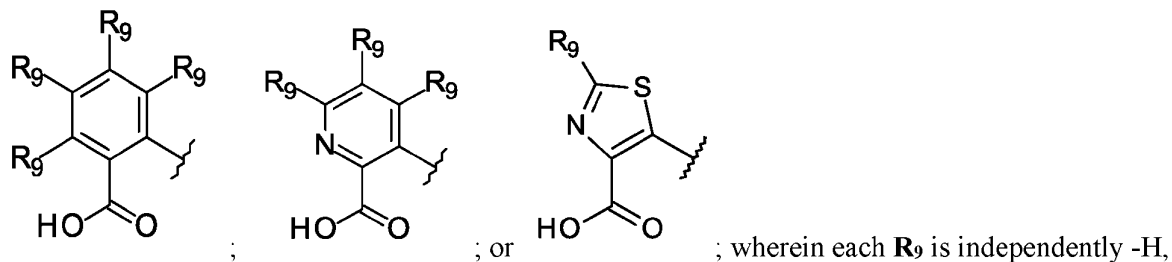


is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl.

Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl.

More preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[556] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

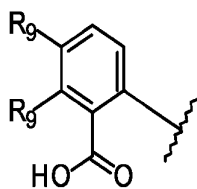


wherein each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl. Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. More preferably each **R₉** is

- 227 -

independently -H, halogen, methyl, or trifluoromethyl.

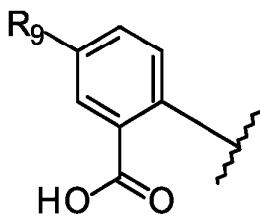
[557] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl.

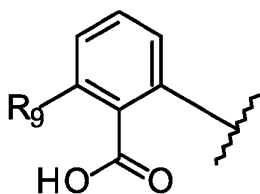
Preferably each **R₉** is independently -H, halogen, methyl or trifluoromethyl.

[558] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl. Preferably **R₉** is -H, or trifluoromethyl.

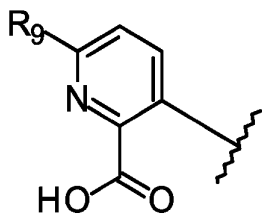
[559] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl. Preferably **R₉** is -H, or halogen. More preferably, **R₉** is -H, or fluoro.

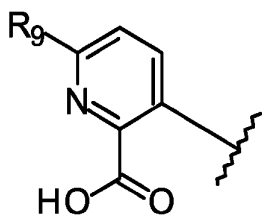
[560] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

- 228 -



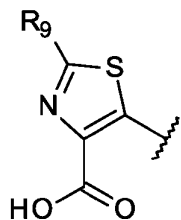
; wherein **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Preferably **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

[561] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl. Preferably **R₉** is halogen or trifluoromethyl. More preferably **R₉** is chloro or trifluoromethyl.

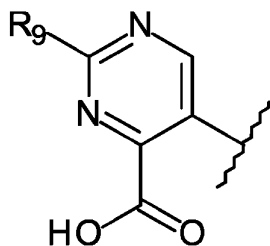
[562] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. Preferably **R₉** is -H, methyl, or trifluoromethyl.

[563] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

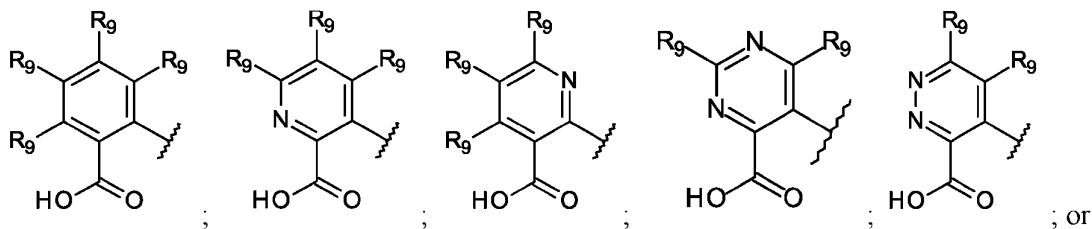
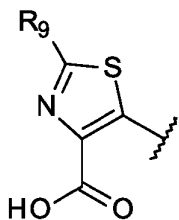
- 229 -



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Preferably **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl.

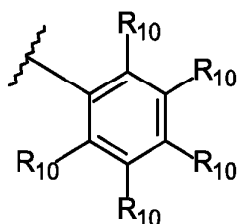
[564] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, each **R₉** is independently H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl.

[565] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



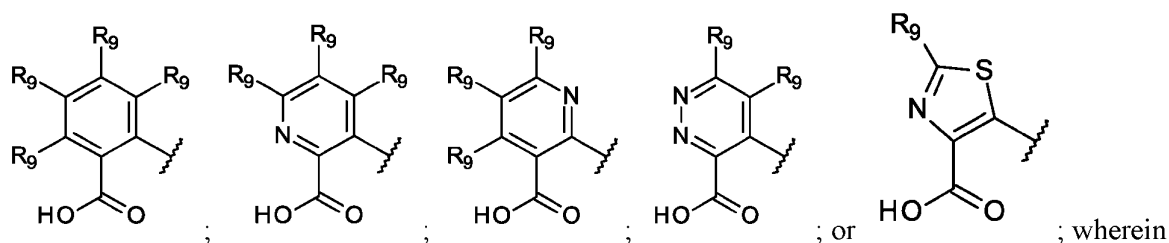
; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:

- 230 -



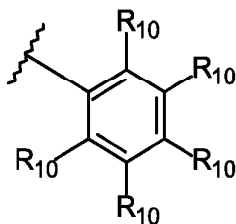
wherein each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl.

[566] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



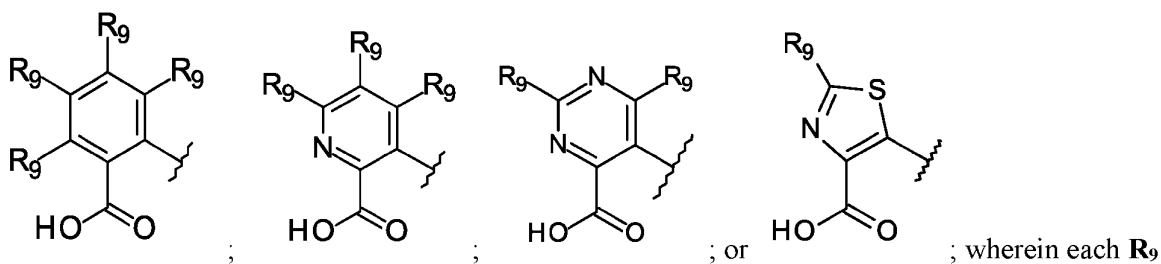
each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:

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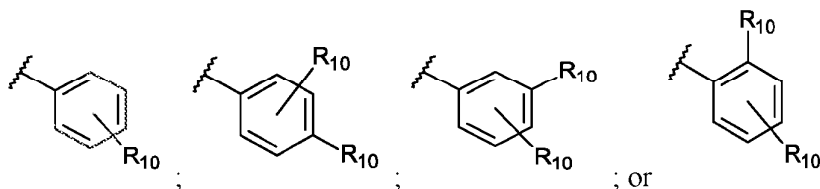
wherein each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN; and each **R**₁₁ is independently -H or C₁-C₃ alkyl.

[567] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



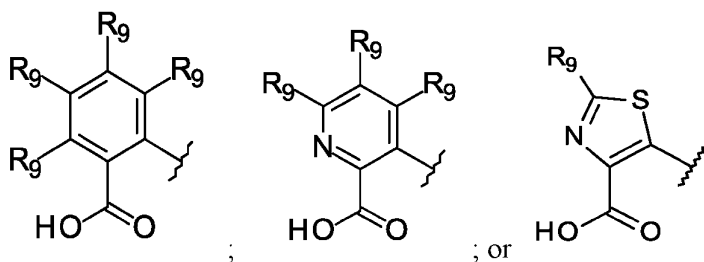
wherein each **R**₉ is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl, and **R**₂ is a group of the formula:

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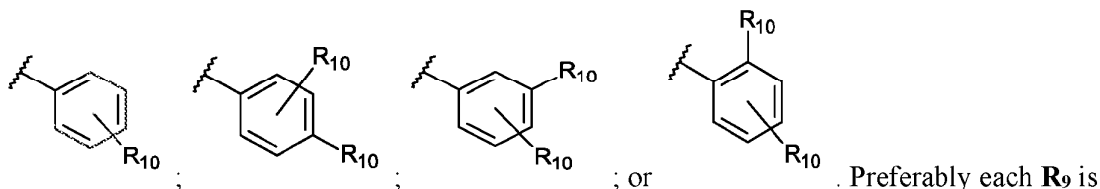
Preferably each **R₉** is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Most preferably each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[568] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



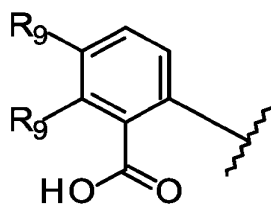
; or ; wherein each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:

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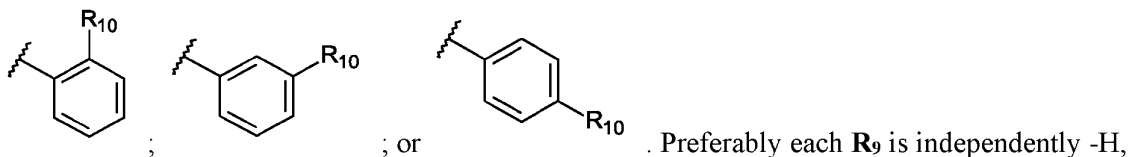


independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. Most preferably each **R₉** is independently -H, halogen, methyl, or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[569] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:

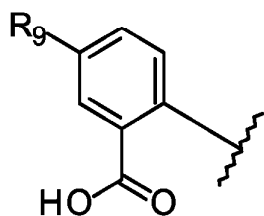


halogen, methyl or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆

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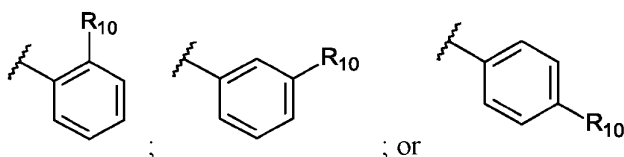
haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[570] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl, and **R₂** is a group of the

formula:



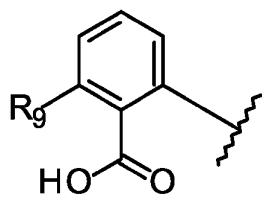
. Preferably **R₉** is -H, or trifluoromethyl.

Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is

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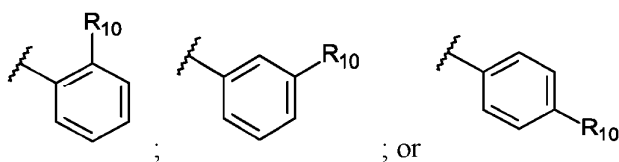
each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[571] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl, and **R₂** is a group of the

formula:

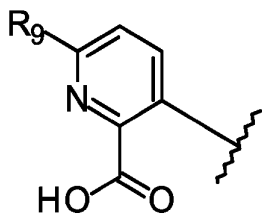


. Preferably **R₉** is -H, or halogen. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

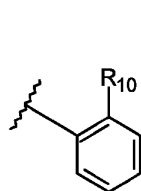
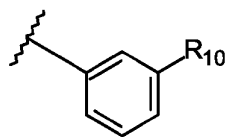
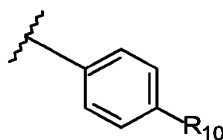
haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[572] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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; wherein **R₉** is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, and **R₂** is a group of the formula:



;

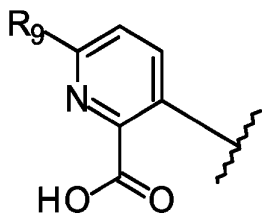
; or

; preferably **R₉** is -H,

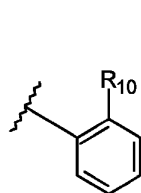
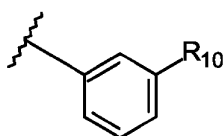
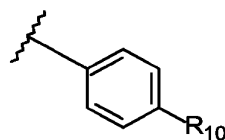
halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[573] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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; wherein **R₉** is halogen, or C₁-C₃ haloalkyl, and **R₂** is a group of the formula:



;

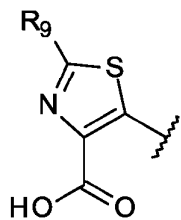
; or

; preferably **R₉** is halogen or

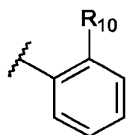
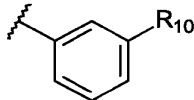
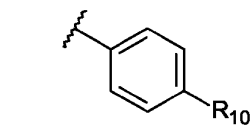
trifluoromethyl. More preferably **R₉** is chloro or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[574] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

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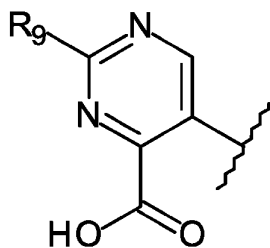
; wherein R_9 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, and R_2 is a group of the formula:



; or . Preferably, each R_{10} is

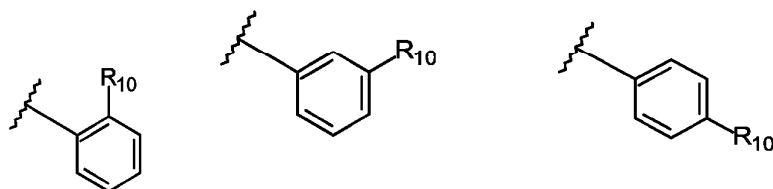
independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-SO_2R_{11}$, $-CONR_{11}R_{11}$, $-NR_{11}R_{11}$, $-NR_{11}-CO_2R_{11}$, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, $-NR_{11}R_{11}$, -OH or -CN.

[575] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, R_1 is a group of the formula:



; wherein R_9 is -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl, and R_2 is a group of the formula:

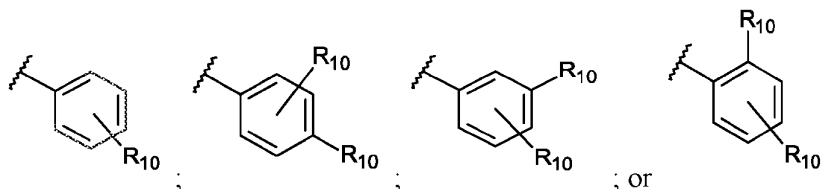
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; or ; preferably R_9 is -H,

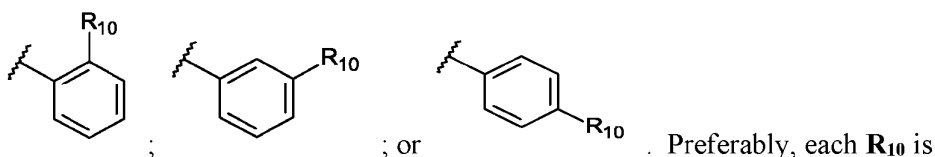
halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[576] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, R_3 is -H, -CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl (preferably R_3 is -H, -CN, or C₁-C₃ alkyl), R_5 is -H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, R_6 is -H or halogen, R_7 is -CN, methyl or trifluoromethyl, and R_2 is a group of the formula:



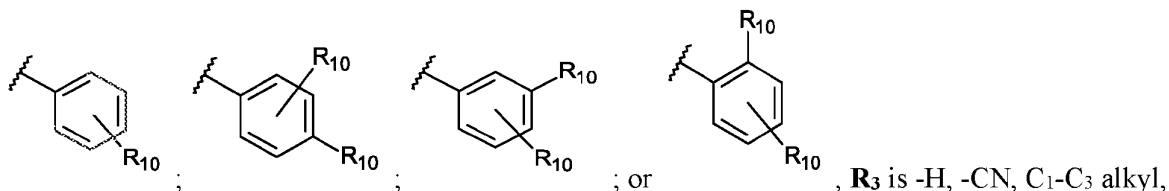
; or ; more preferably R_3 is -H, or methyl, R_5 is -H, halogen, methyl, or trifluoromethyl, R_6 is -H, R_7 is methyl, and R_2 is a group of the formula:

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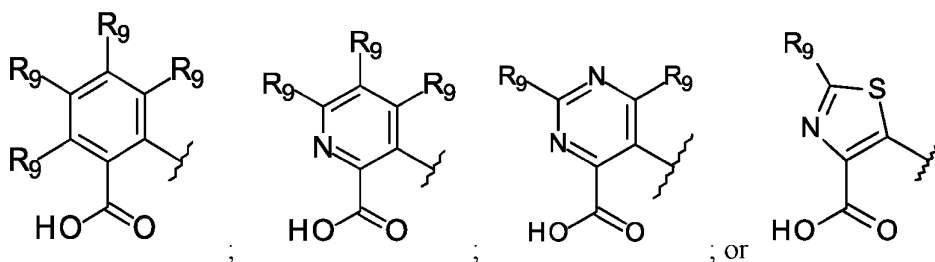


Preferably, each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[577] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, R_2 is a group of the formula:



R_3 is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, R_5 is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, R_6 is -H or halogen, and R_1 is a group of the formula:

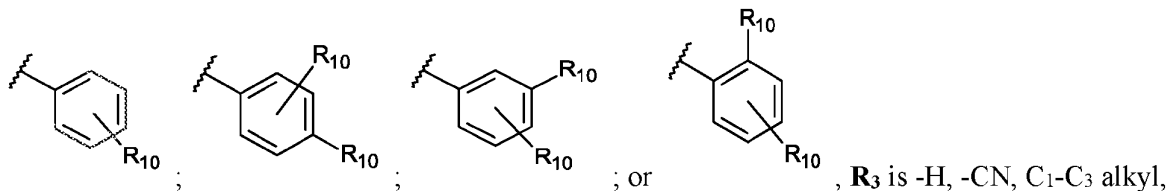


wherein each R_9 is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Preferably R_3 is -H,

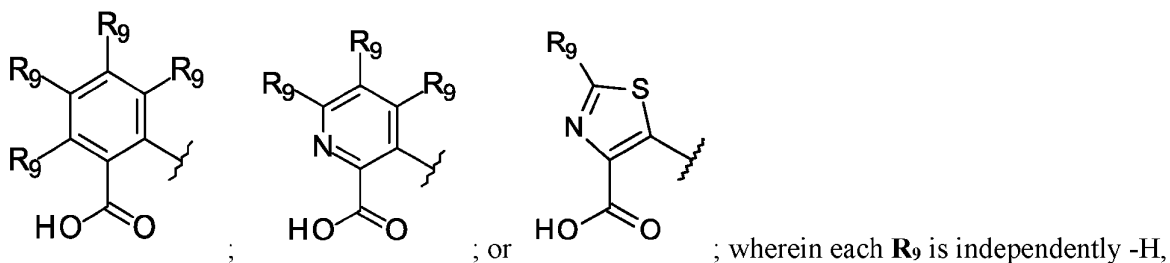
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methyl, or trifluoromethyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and each **R₉** is independently -H, halogen, methyl, trifluoromethyl, or cyclopropyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[578] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₂** is a group of the formula:



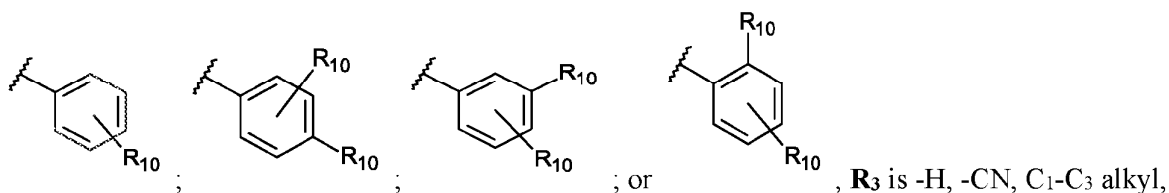
, **R₃** is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R₃** is -H, -CN, or C₁-C₃ alkyl), **R₅** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₆** is -H or halogen, and **R₁** is a group of the formula:



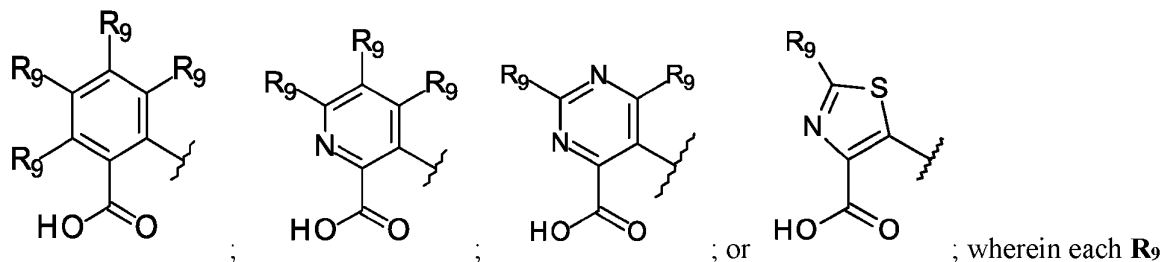
; wherein each **R₉** is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. More preferably **R₃** is -H, or methyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and each **R₉** is independently -H, halogen, methyl, or trifluoromethyl. Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆

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alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN. [579] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:

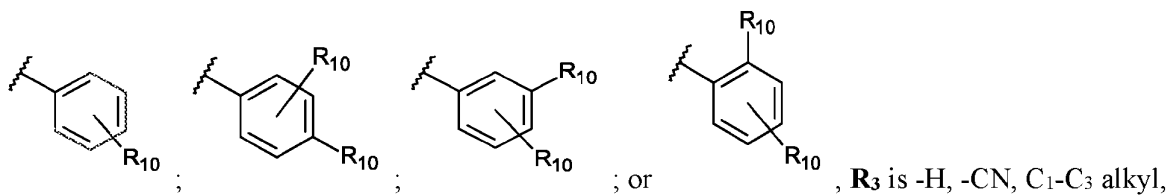


; wherein each **R**₉ is independently -H, halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₃-C₅ cycloalkyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole,

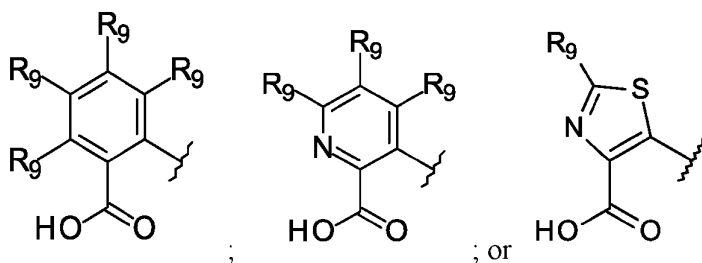
- 243 -

or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[580] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₂ is a group of the formula:



, **R**₃ is -H, -CN, C₁-C₃ alkyl, or C₁-C₃ haloalkyl (preferably **R**₃ is -H, -CN, or C₁-C₃ alkyl), **R**₅ is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R**₆ is -H or halogen, **R**₇ is -CN, methyl or trifluoromethyl, and **R**₁ is a group of the formula:

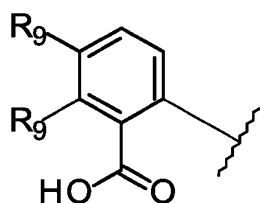


wherein each **R**₉ is independently -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy,

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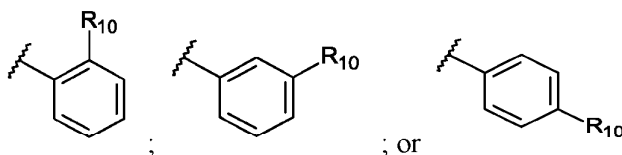
C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[581] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein each **R₉** is independently -H, halogen, methyl or trifluoromethyl,

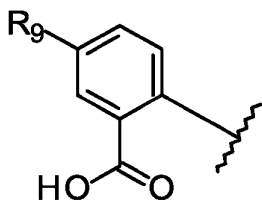
R₂ is a group of the formula:



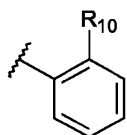
, **R₃** is -H, methyl, or trifluoromethyl, **R₅** is -H, halogen, methyl or trifluoromethyl, **R₆** is -H, or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[582] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

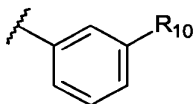
- 245 -



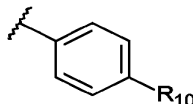
; wherein **R₉** is -H, halogen, or trifluoromethyl, (preferably **R₉** is -H, or trifluoromethyl), **R₂** is a group of the formula:



;

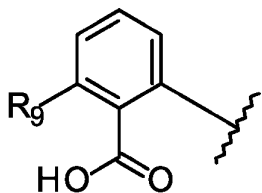


; or



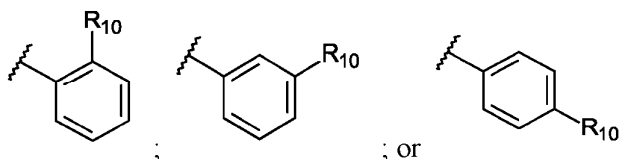
, **R₃** is -H, or methyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[583] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, or C₁-C₃ haloalkyl (preferably **R₉** is -H, or halogen), **R₂** is a group of the formula:

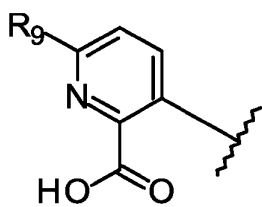
- 246 -



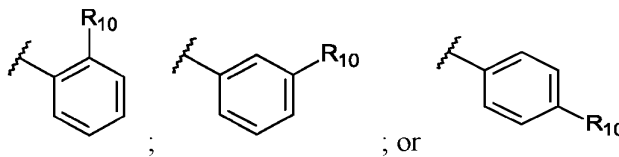
; or , **R₃** is -H, or methyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl).

Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[584] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl, **R₂** is a group of the formula:

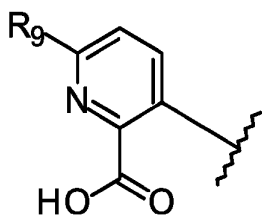


; or , **R₃** is -H, methyl, or trifluoromethyl, **R₅** is -H, halogen, methyl or trifluoromethyl, **R₆** is -H, or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy,

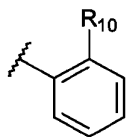
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C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

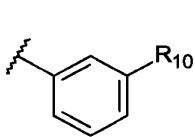
[585] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R**₁ is a group of the formula:



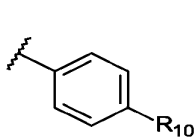
; wherein **R**₉ is -H, halogen, or trifluoromethyl, (preferably **R**₉ is halogen or trifluoromethyl), **R**₂ is a group of the formula:



;



; or



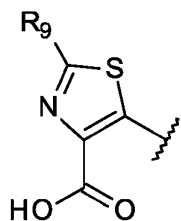
, **R**₃ is -H, or methyl, **R**₅ is -H, halogen, methyl, or trifluoromethyl, **R**₆ is -H or halogen, and **R**₇ is C₁-C₃ alkyl (preferably methyl).

Preferably, each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is

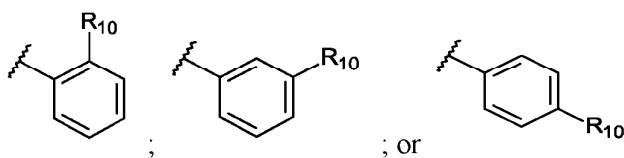
- 248 -

each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

[586] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:



; wherein **R₉** is -H, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl, **R₂** is a group of the formula:

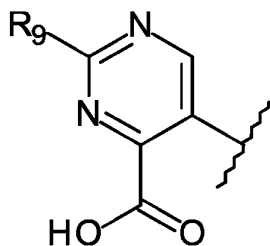


; or , **R₃** is -H, or methyl, **R₅** is -H, halogen, methyl, or trifluoromethyl, **R₆** is -H or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl).

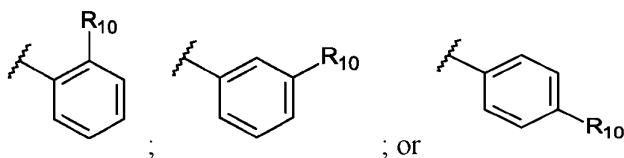
Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

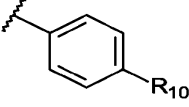
[587] In yet a further compound of Formula (III), or pharmaceutically acceptable salts thereof, **R₁** is a group of the formula:

- 249 -

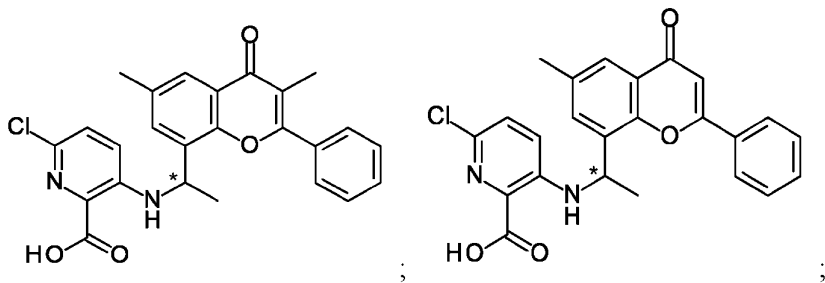


; wherein **R₉** is -H, halogen, methyl, trifluoromethyl, or cyclopropyl, **R₂** is a group of the formula:

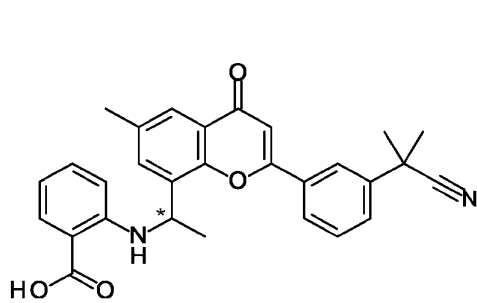
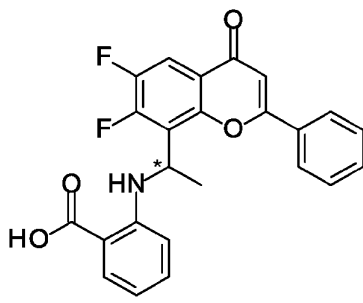
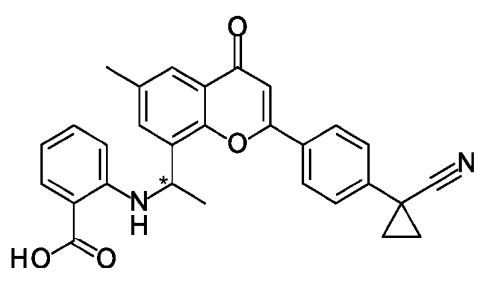
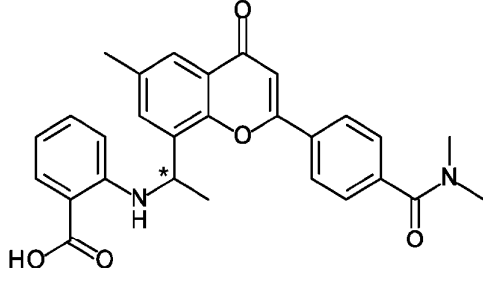
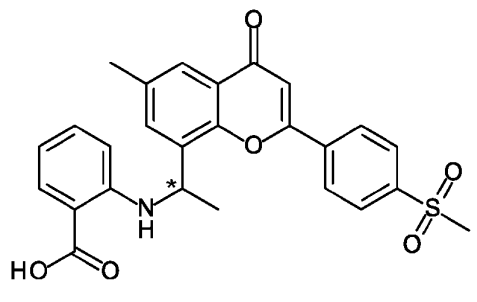
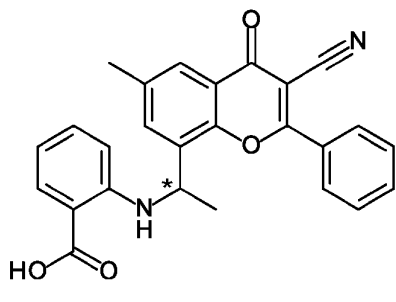
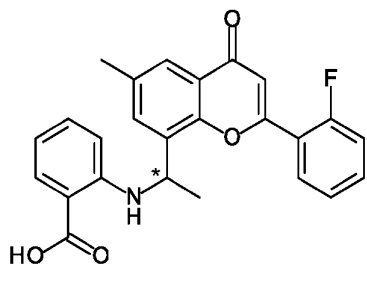
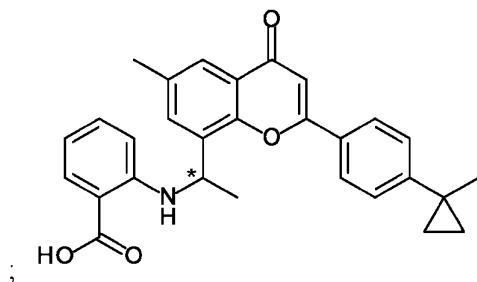


; or  , **R₃** is -H, methyl, or trifluoromethyl, **R₅** is -H, halogen, methyl or trifluoromethyl, **R₆** is -H, or halogen, and **R₇** is C₁-C₃ alkyl (preferably methyl). Preferably, each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl is optionally substituted with a -CN, -OH, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -NR₁₁R₁₁, -OH or -CN.

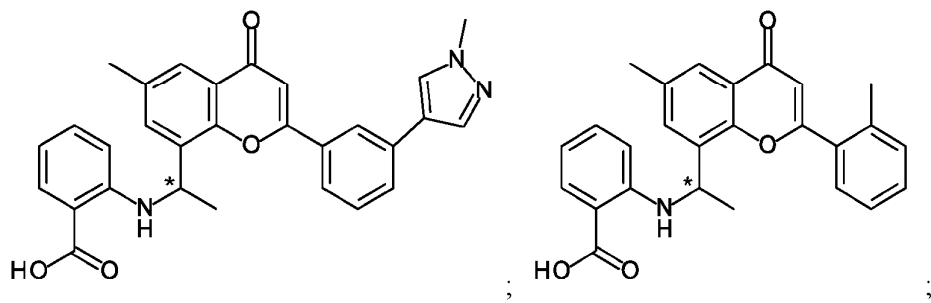
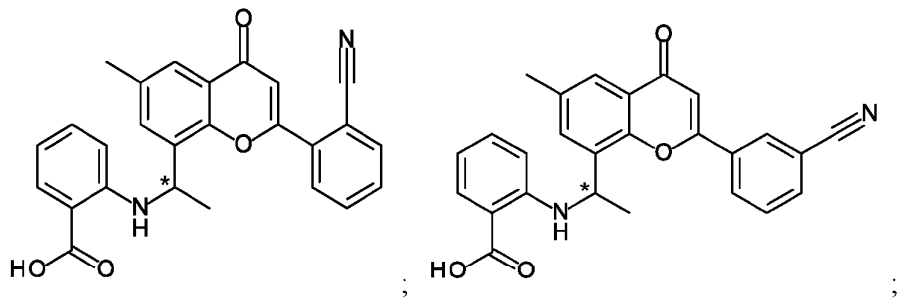
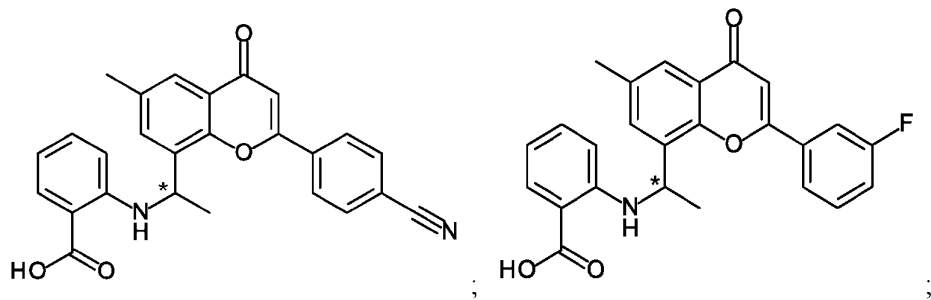
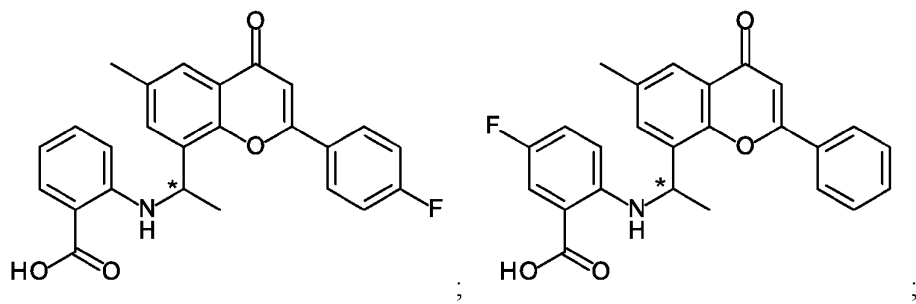
[588] In yet a further compound of Formula (I), the compound is selected from:



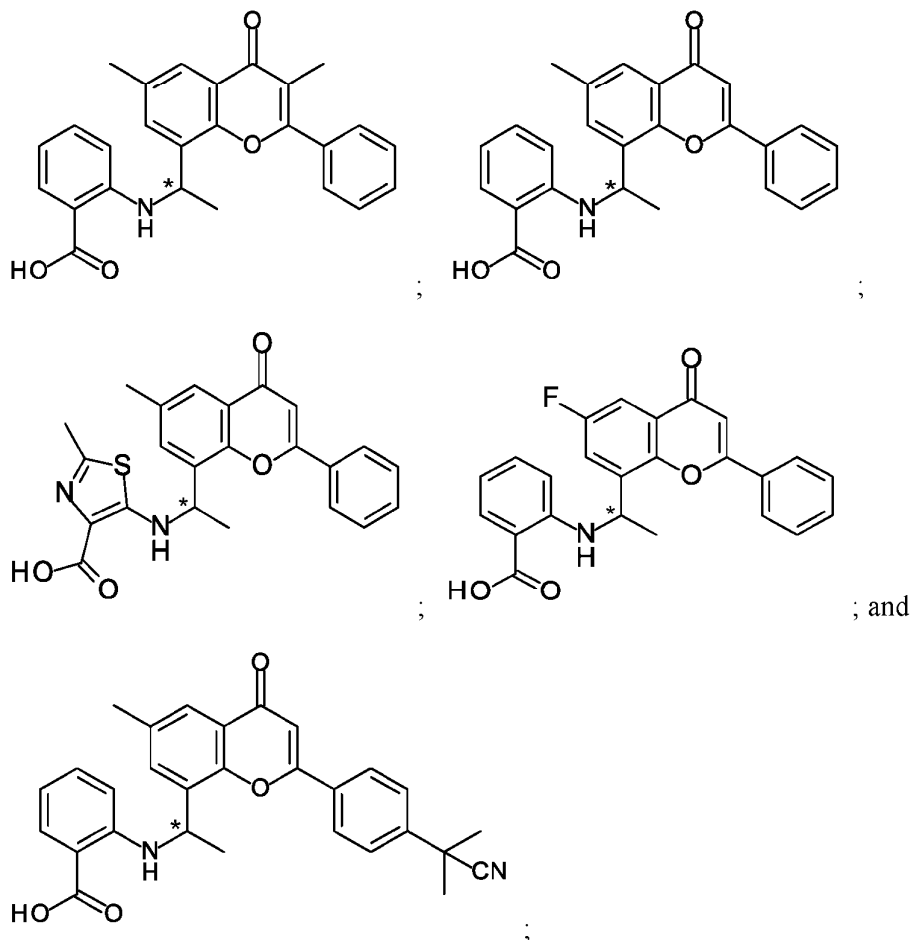
- 250 -



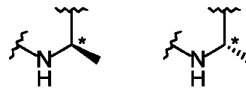
- 251 -



- 252 -



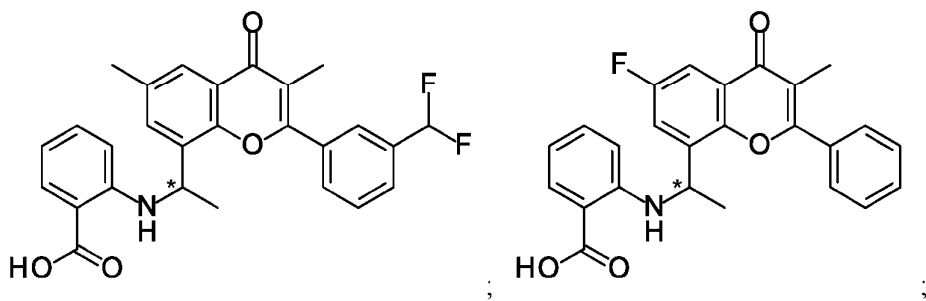
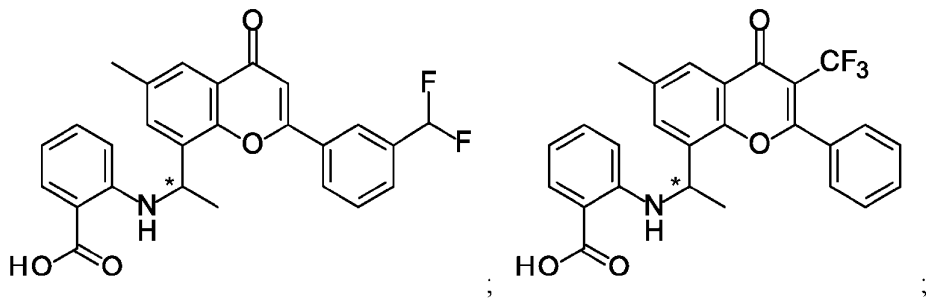
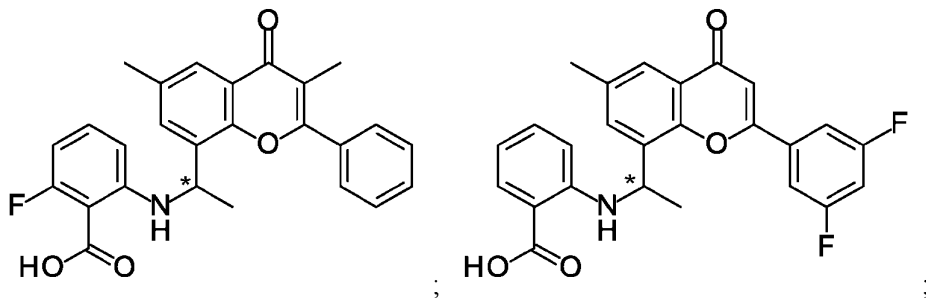
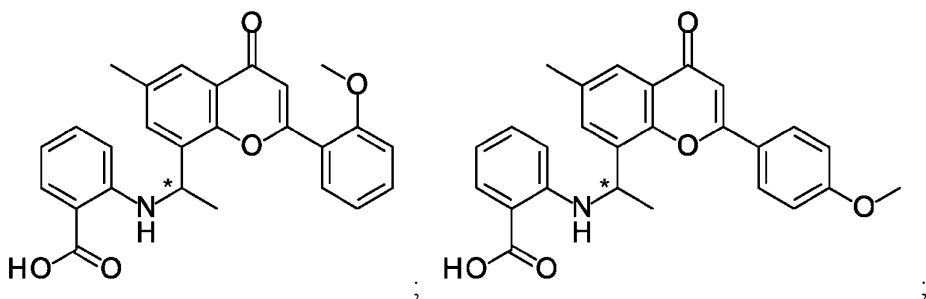
or a pharmaceutically acceptable salt of any of the foregoing;



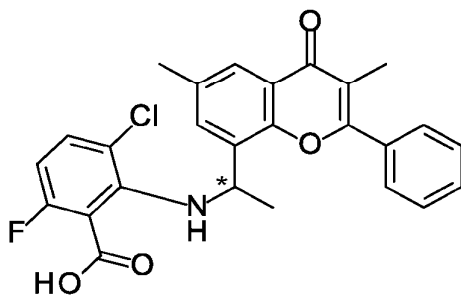
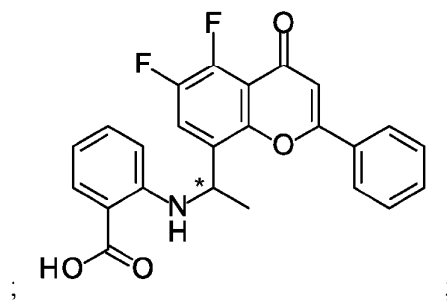
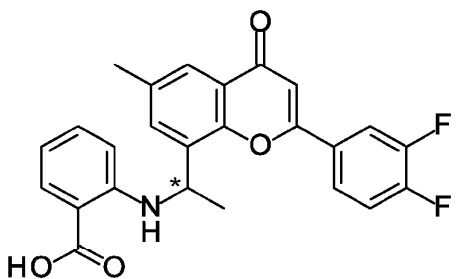
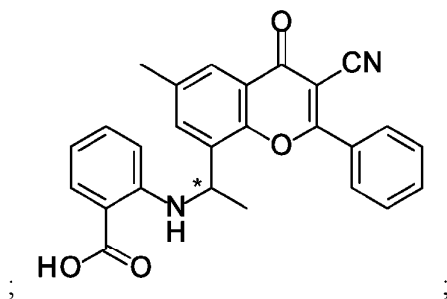
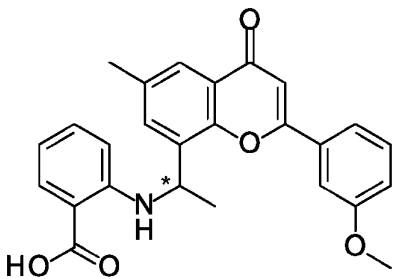
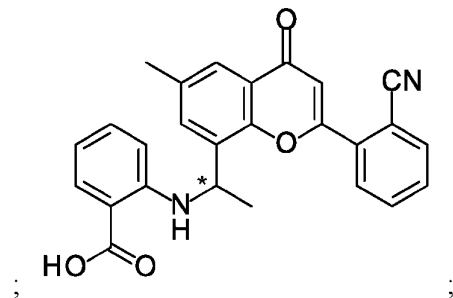
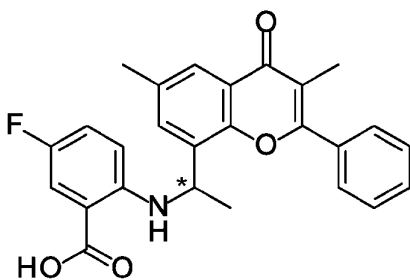
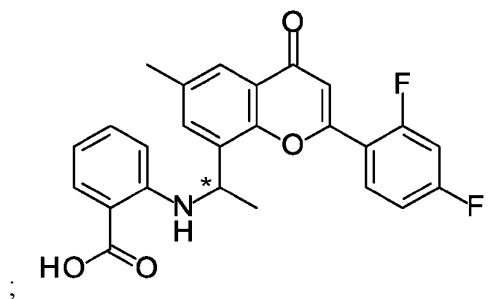
wherein the bond at the * position is as represented,

[589] In yet a further compound of Formula (I), the compound is selected from:

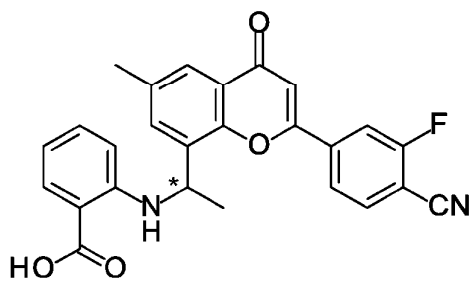
- 253 -



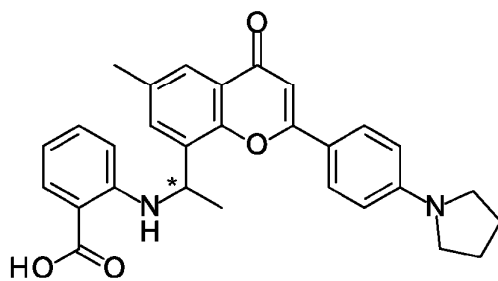
- 254 -



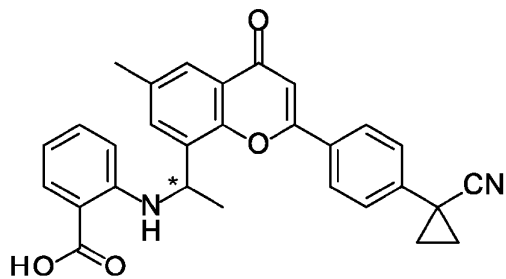
- 255 -



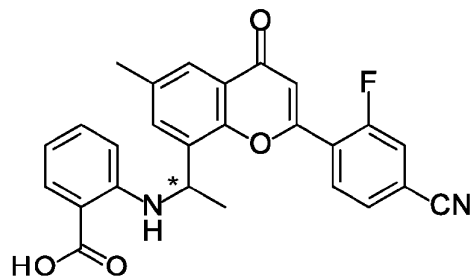
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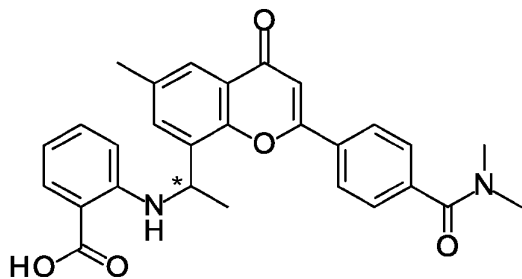
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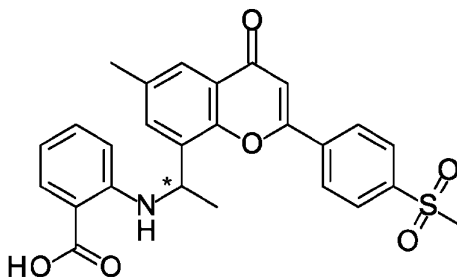
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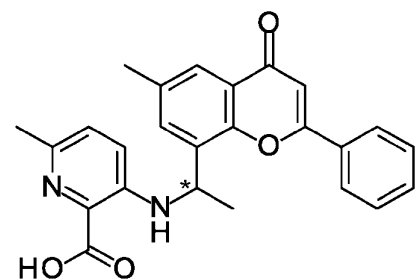
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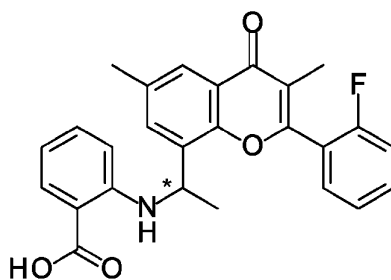
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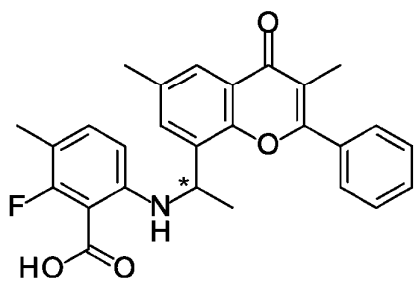
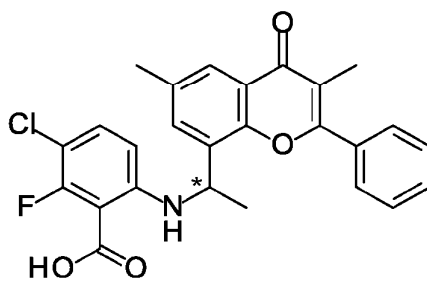
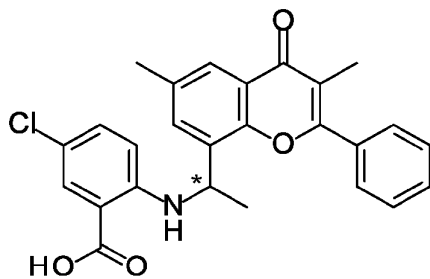
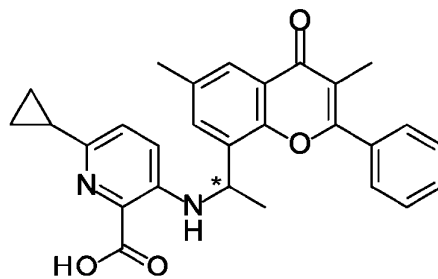
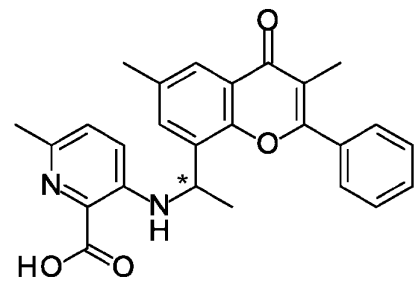
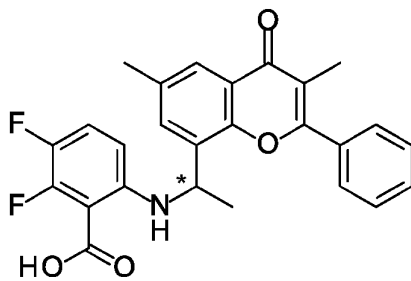
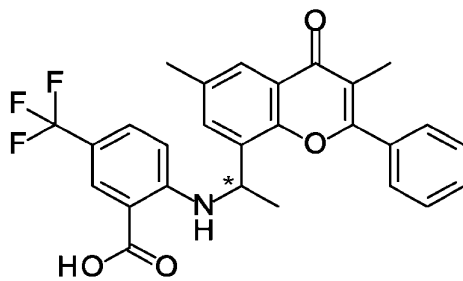
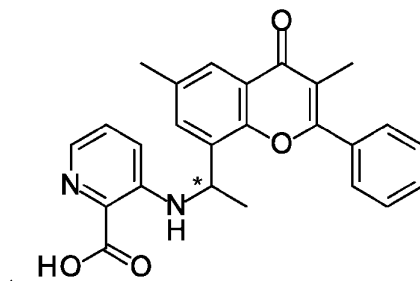


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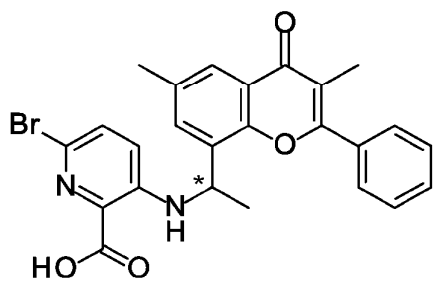
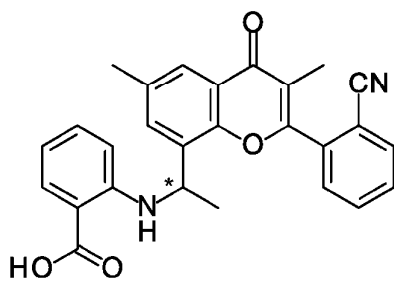
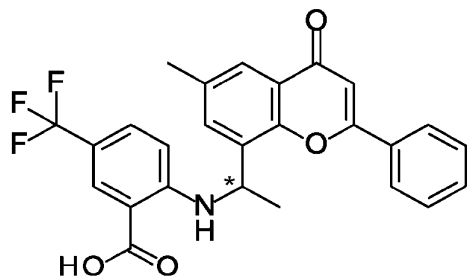
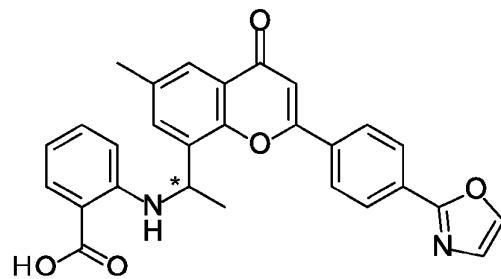
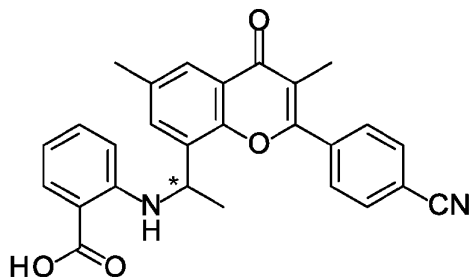
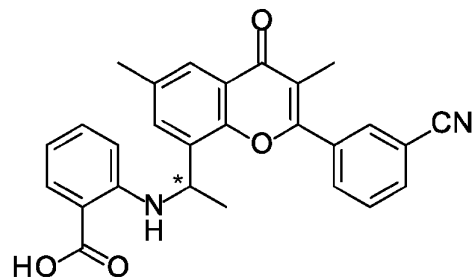
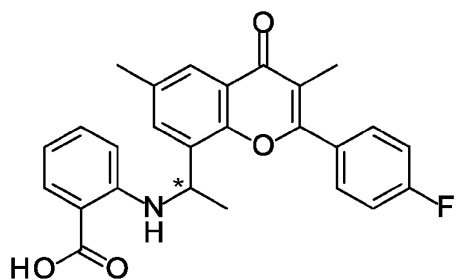
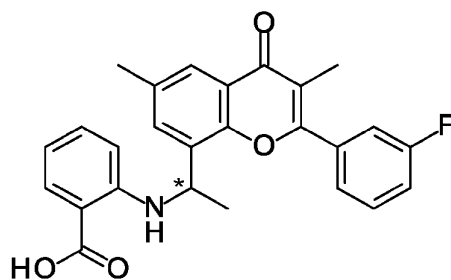


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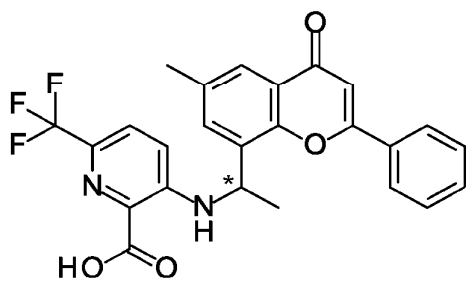
- 256 -



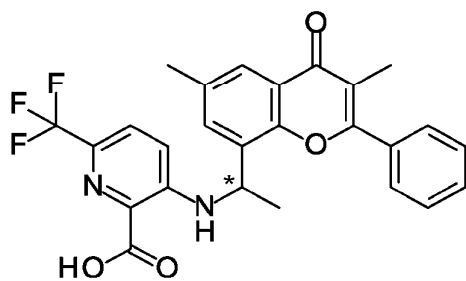
- 257 -



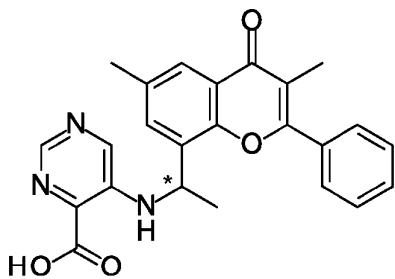
- 258 -



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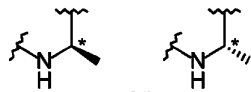


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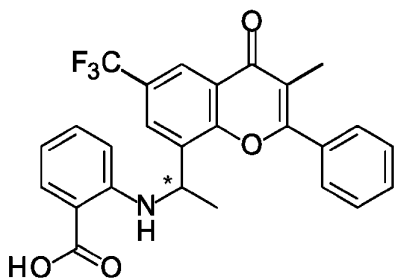
;

or a pharmaceutically acceptable salt of any of the foregoing;

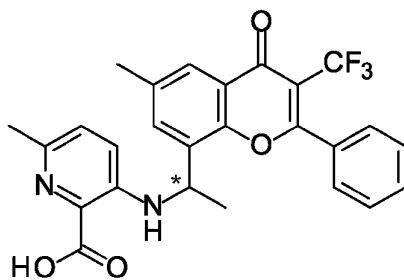


wherein the bond at the * position is as represented, , or .

[590] In yet a further compound of Formula (I), the compound is selected from:

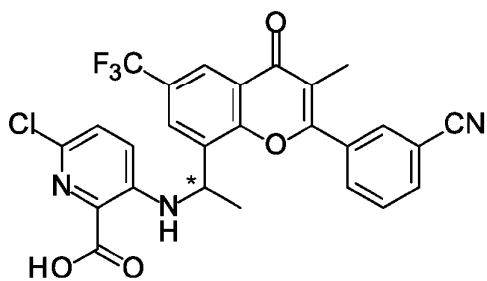


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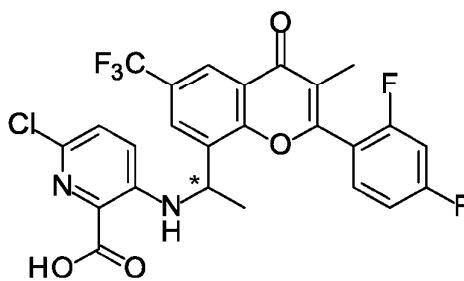


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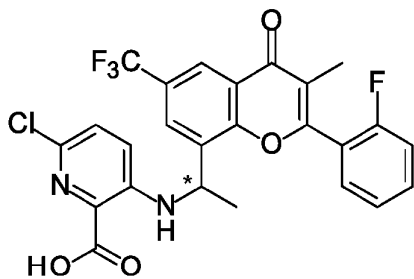
- 259 -



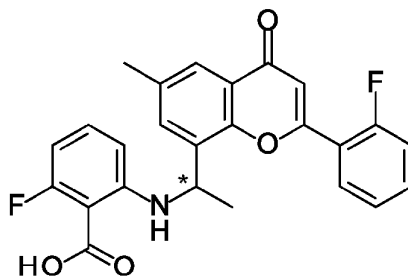
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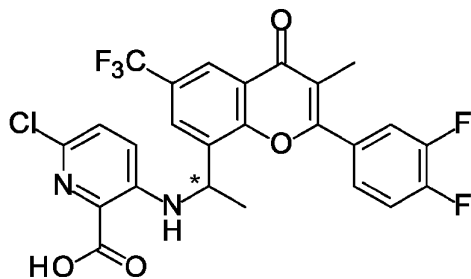
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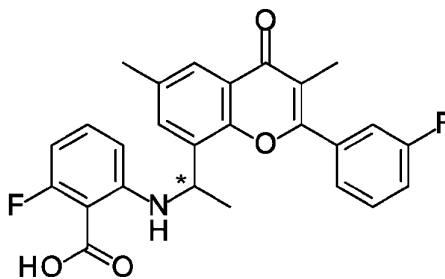
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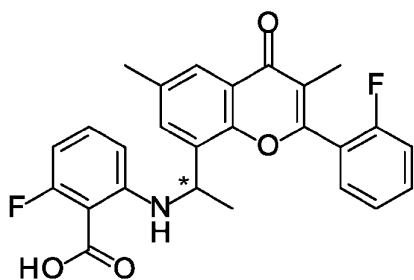
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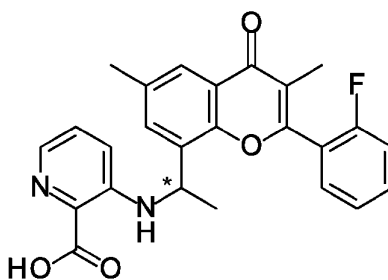
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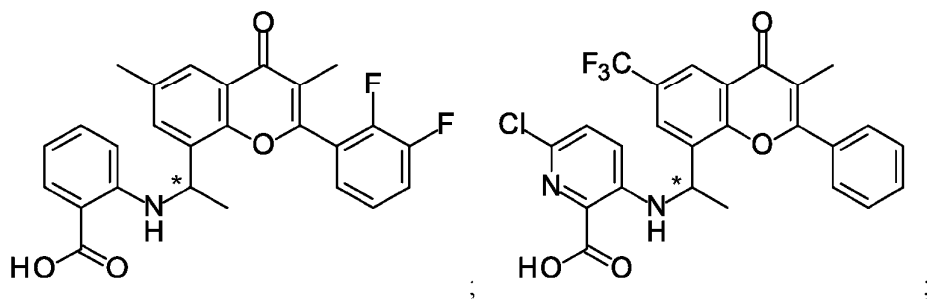
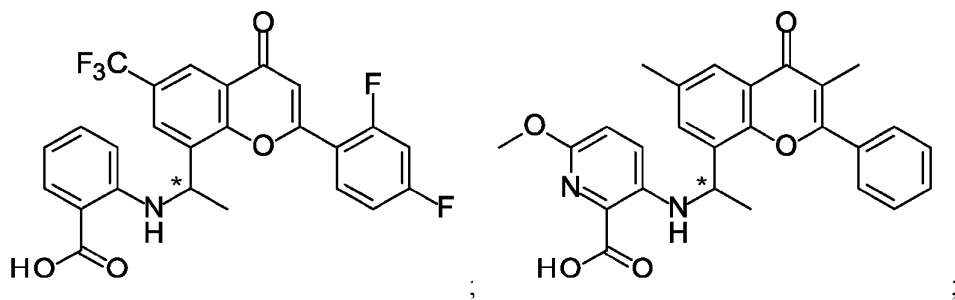
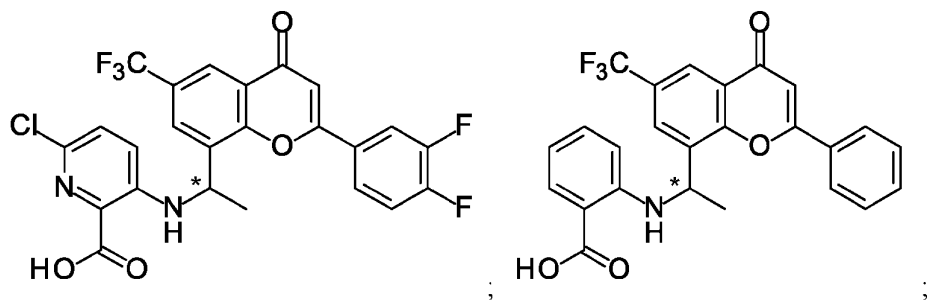
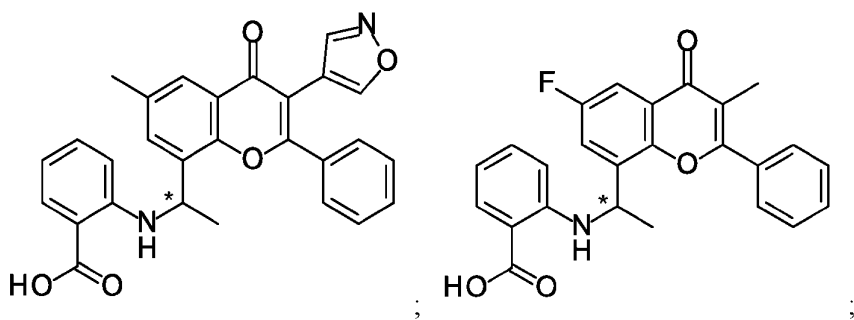


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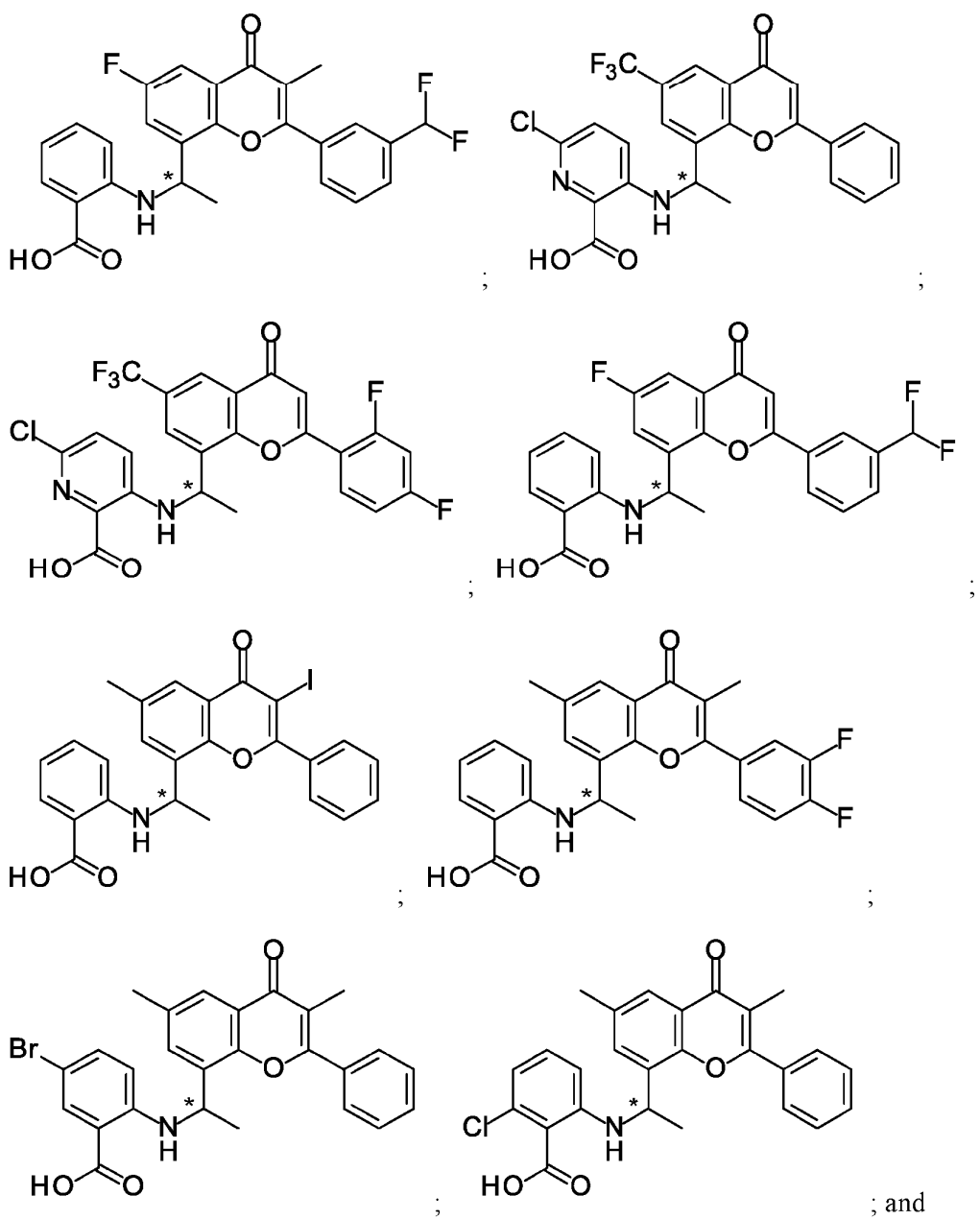


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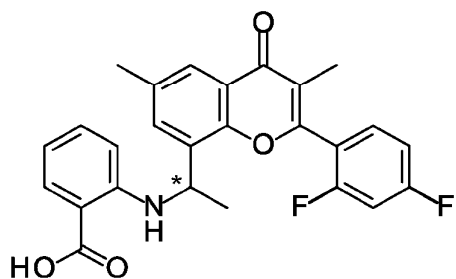
- 260 -



- 261 -

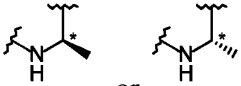


- 262 -

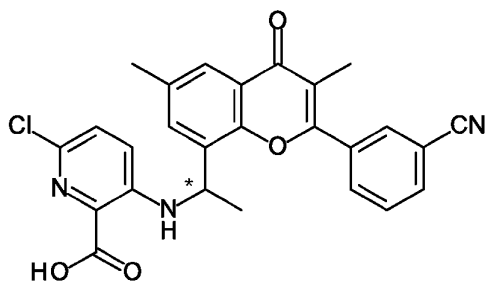


;

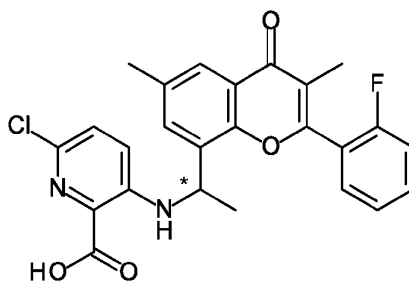
or a pharmaceutically acceptable salt of any of the foregoing;

wherein the bond at the * position is as represented, , or .

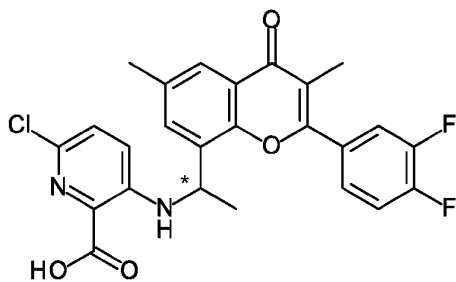
[591] In yet a further compound of Formula (I), the compound is selected from:



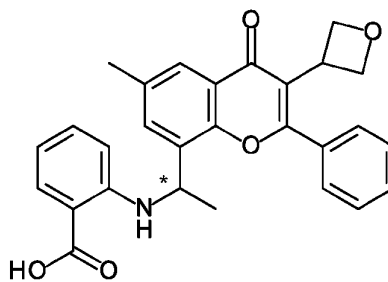
;



;

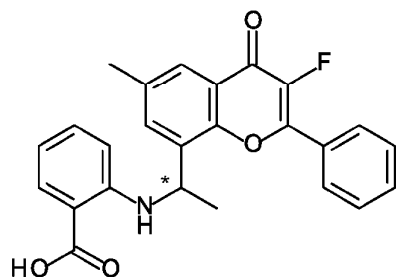


;



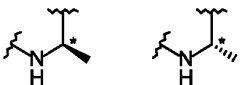
; and

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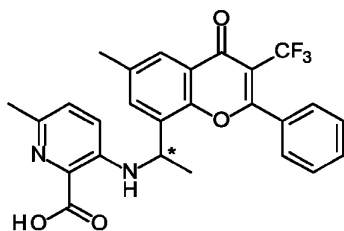


;

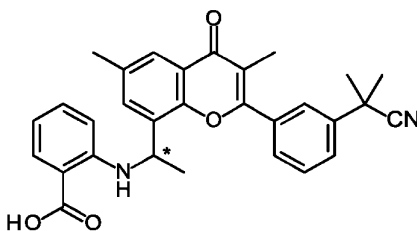
or a pharmaceutically acceptable salt of any of the foregoing;

wherein the bond at the * position is as represented, , or .

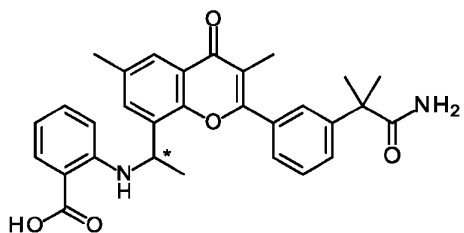
[592] In yet a further compound of Formula (I), the compound is selected from:



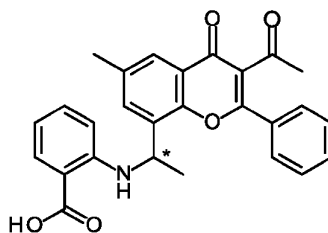
;



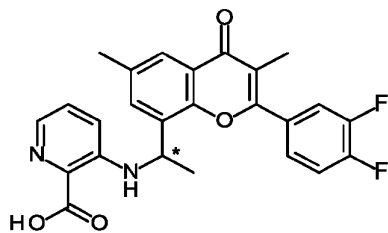
;



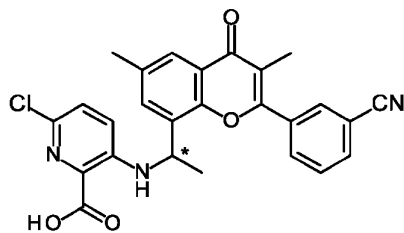
;



;

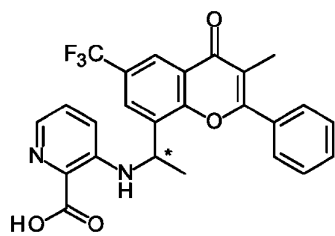


;

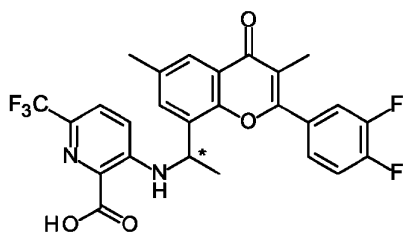


;

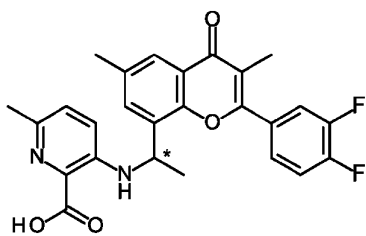
- 264 -



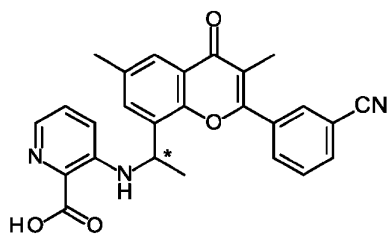
;



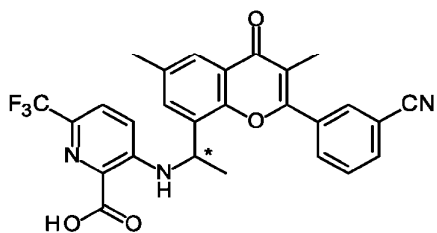
;



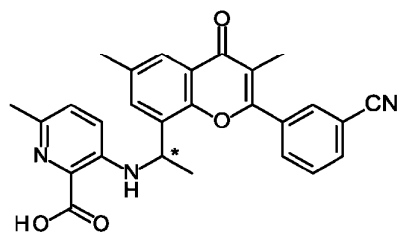
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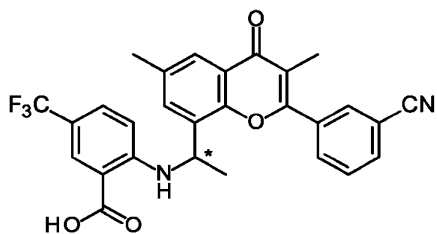
;



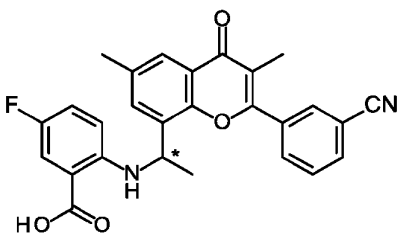
;



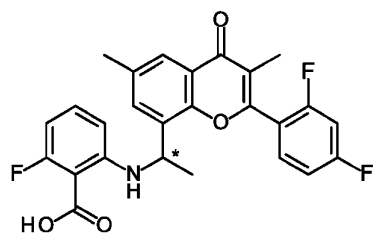
;



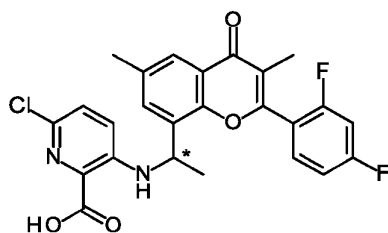
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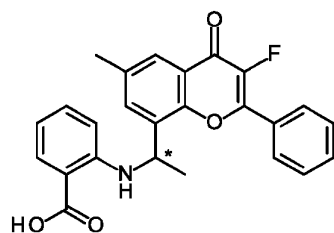
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;

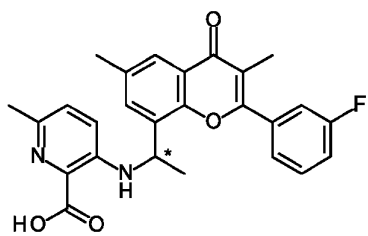


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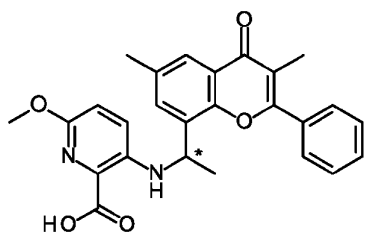


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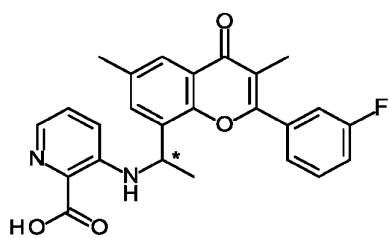
- 265 -



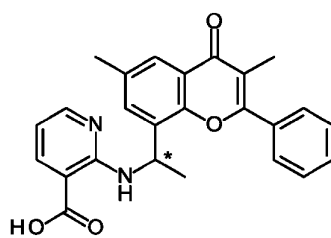
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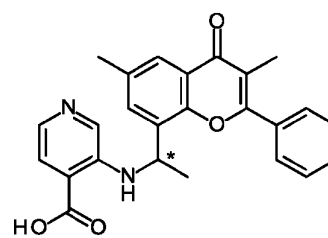
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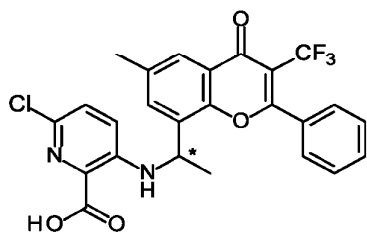
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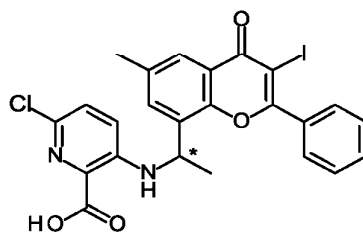
;



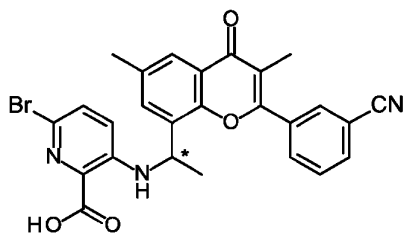
;



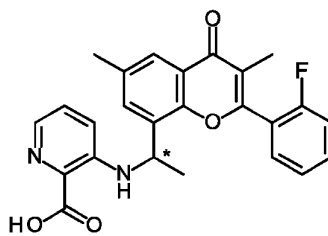
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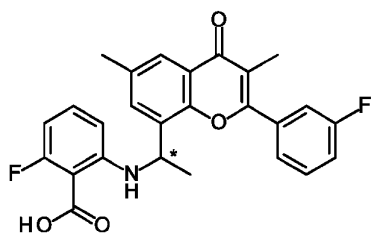
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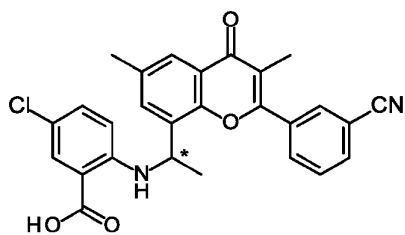
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;

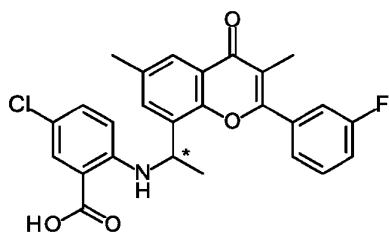


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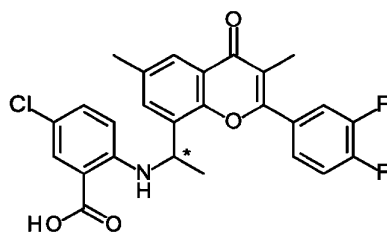


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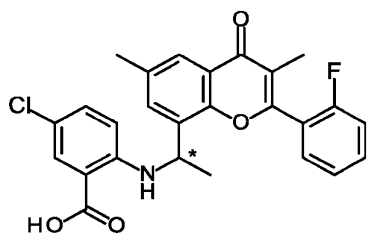
- 266 -



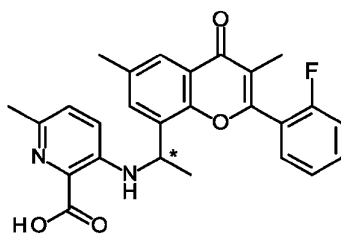
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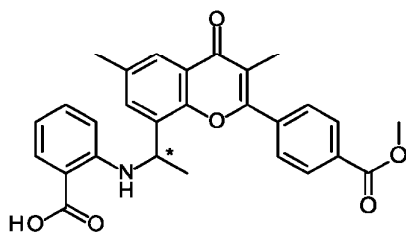
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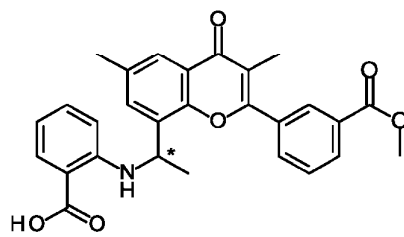
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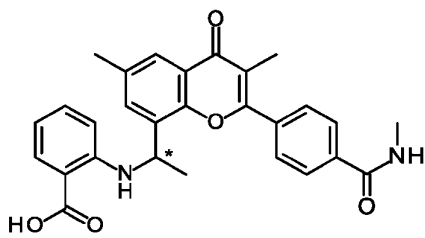
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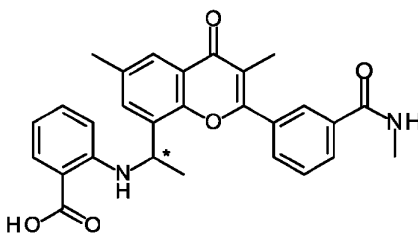
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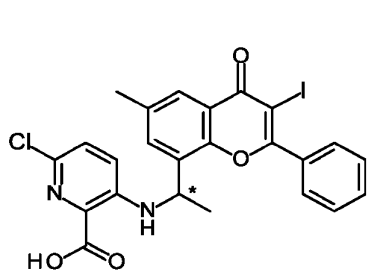
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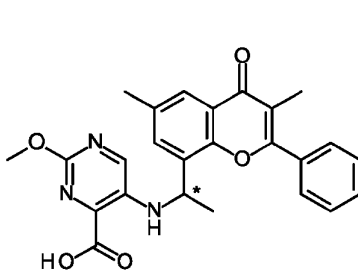
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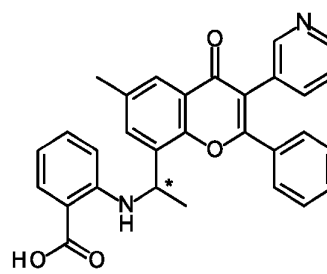
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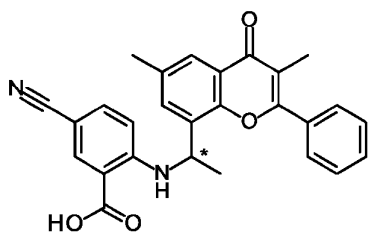


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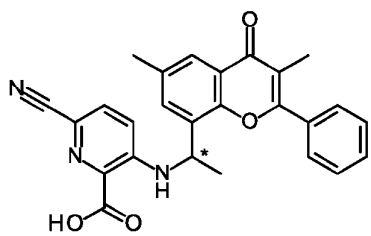


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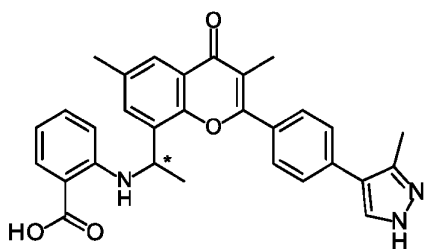
- 267 -



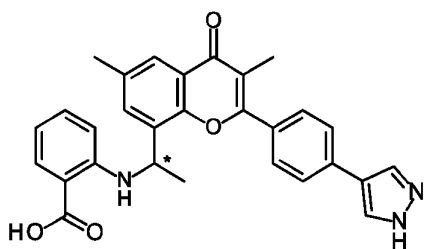
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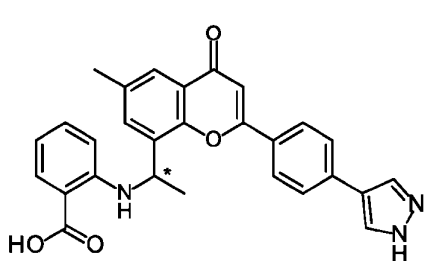
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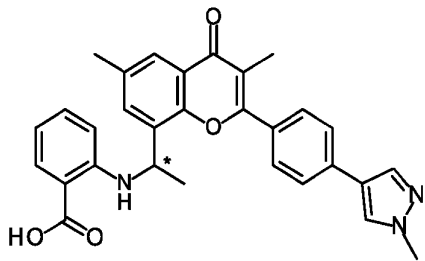
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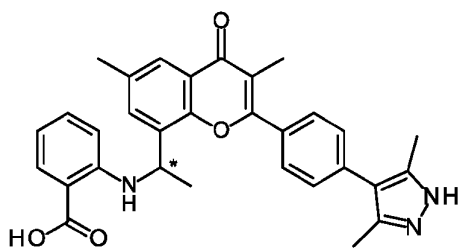
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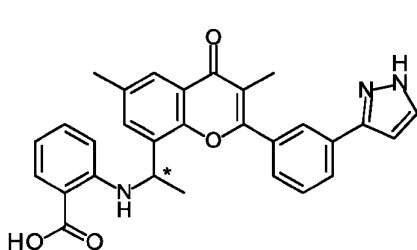
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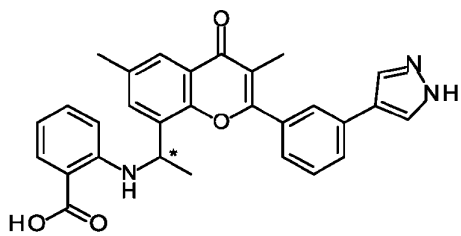
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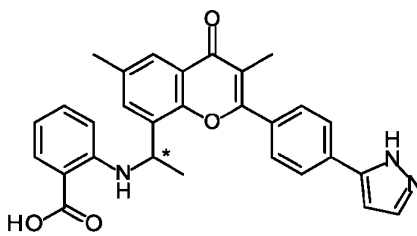
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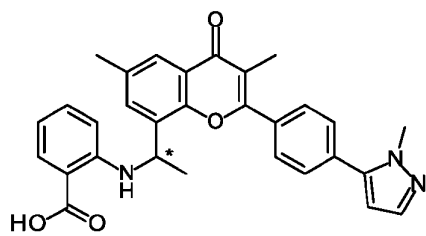


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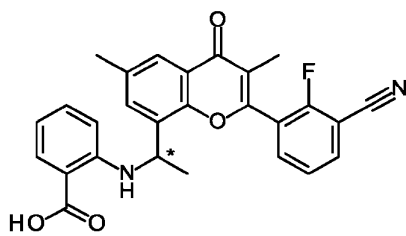


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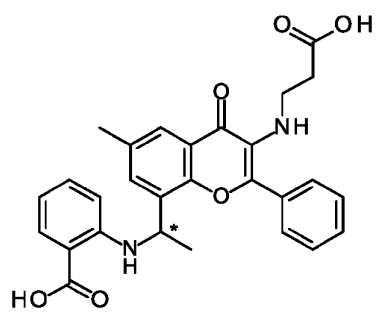
- 268 -



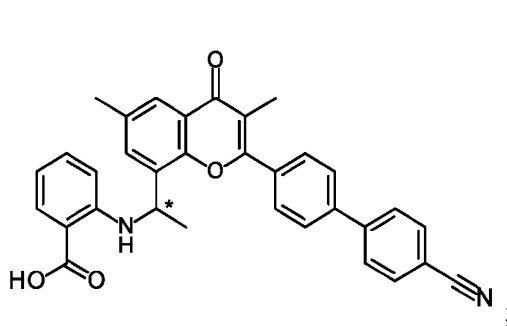
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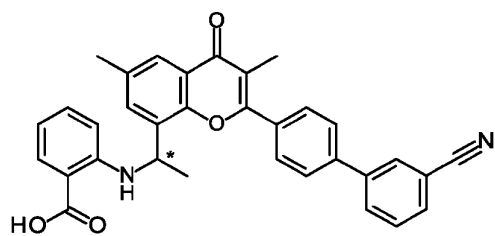
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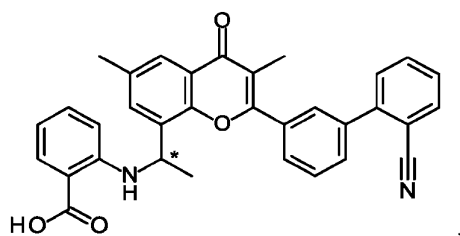
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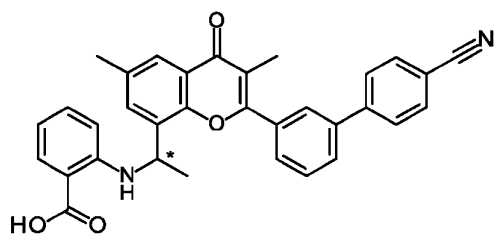
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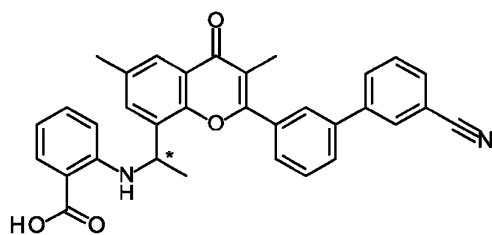
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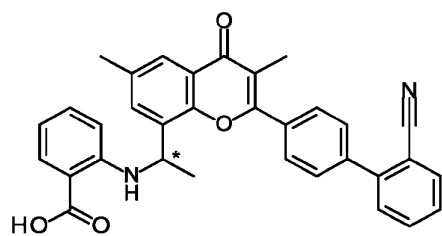
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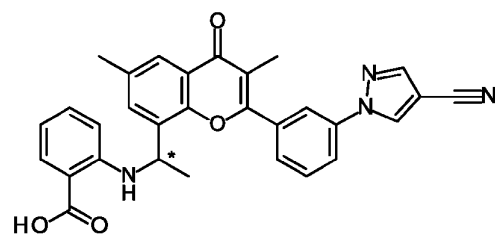
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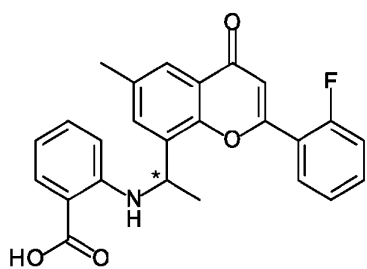


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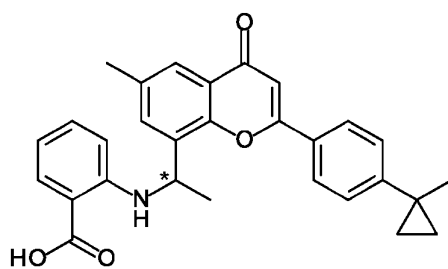


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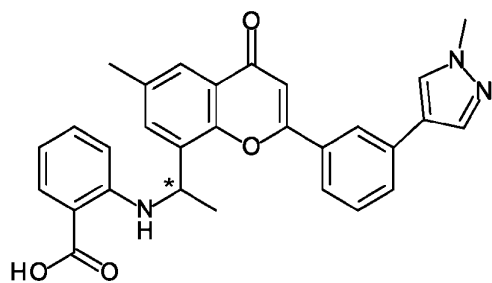
- 270 -



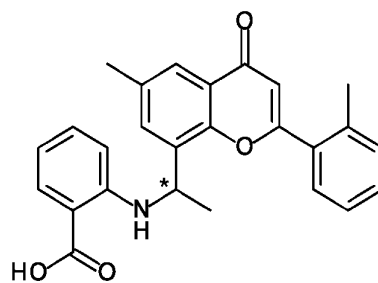
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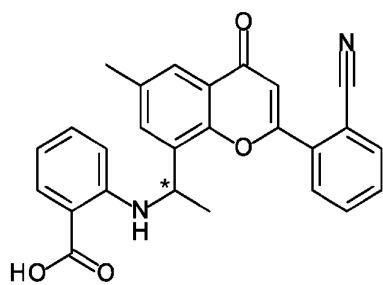
;



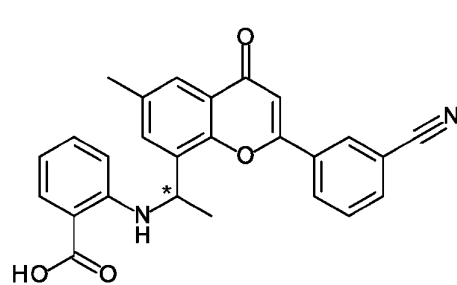
;



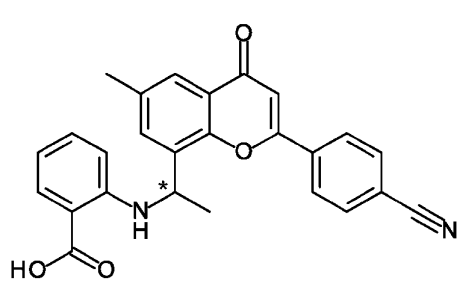
;



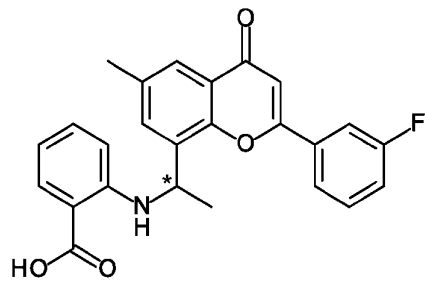
;



;

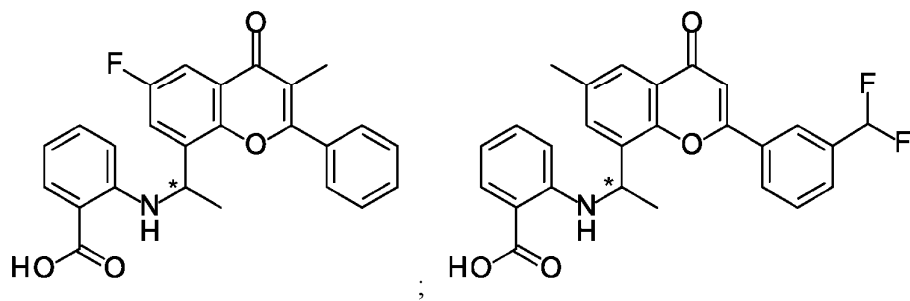
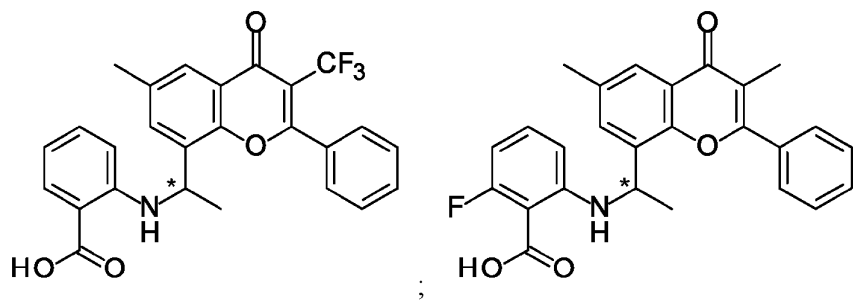
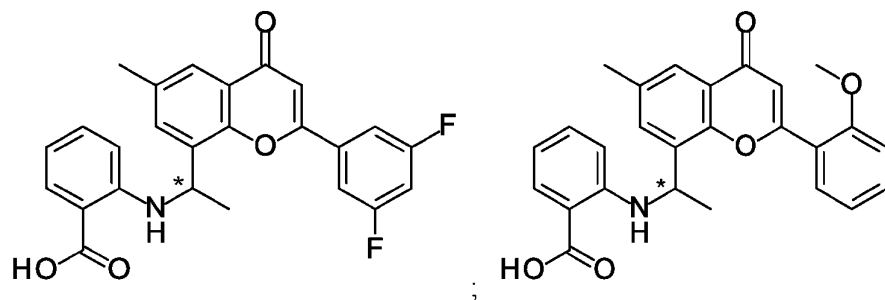
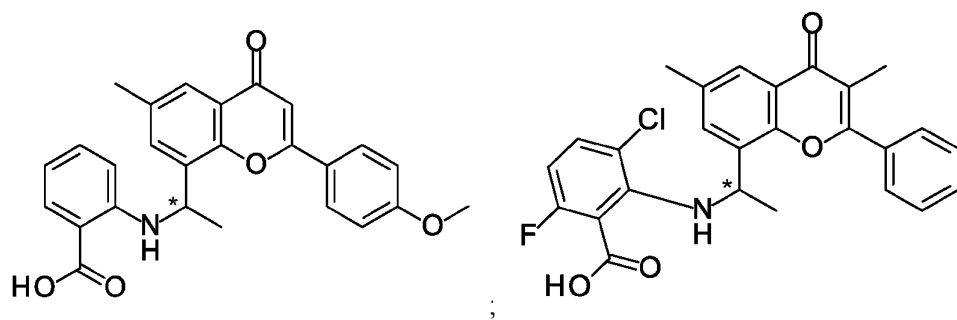


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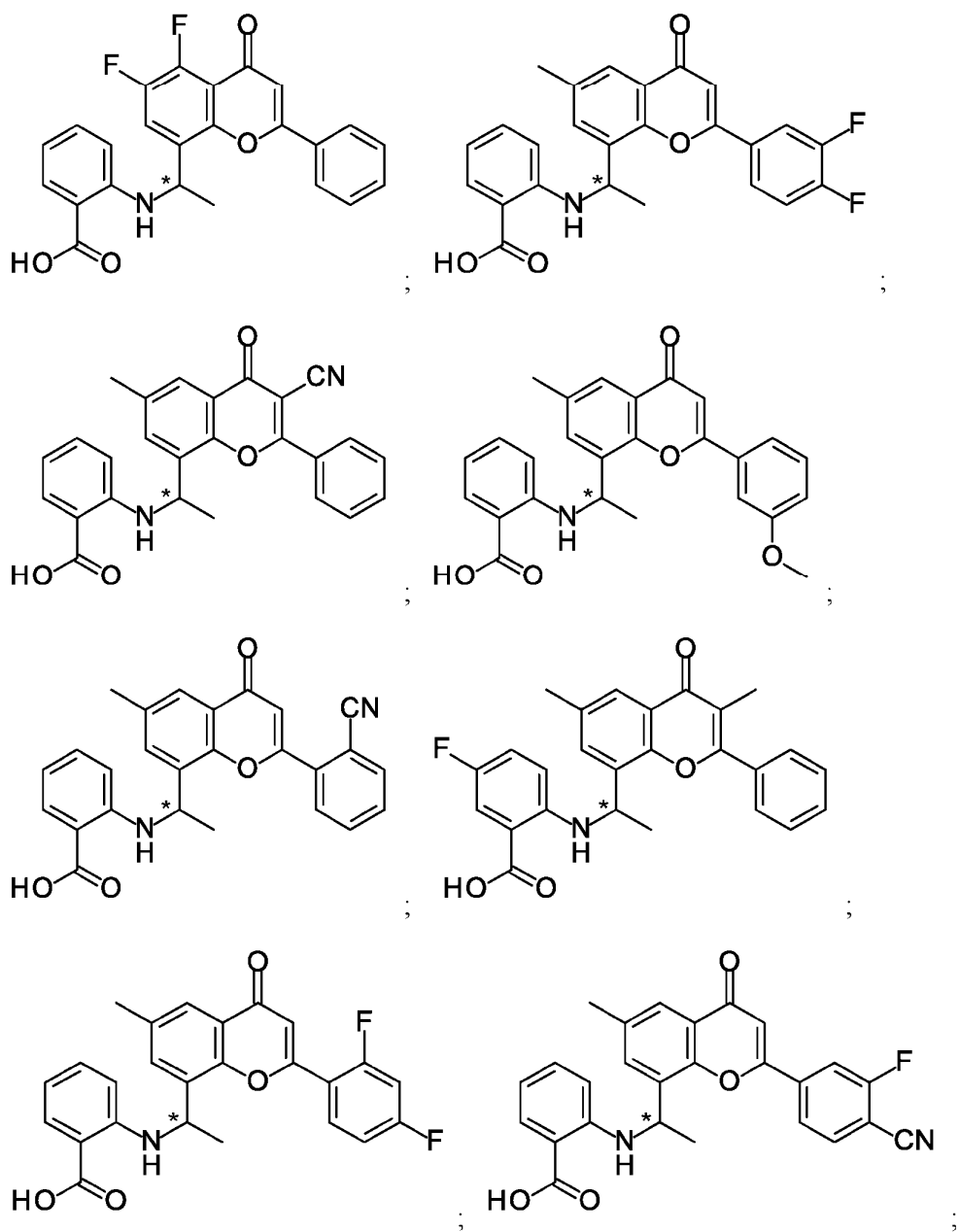


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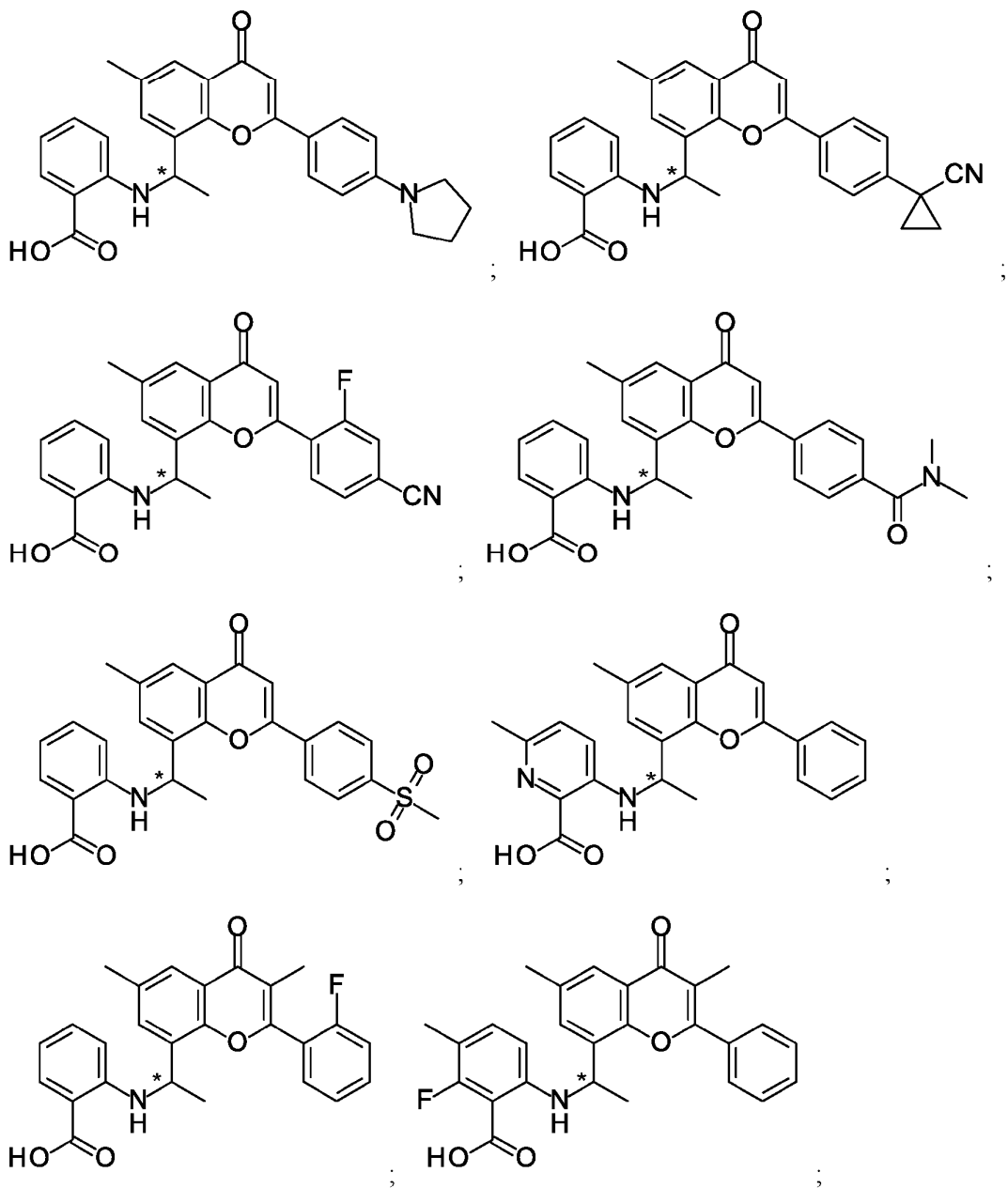
- 272 -



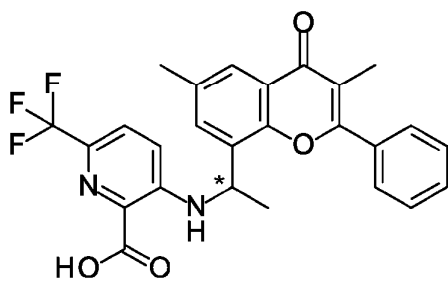
- 273 -



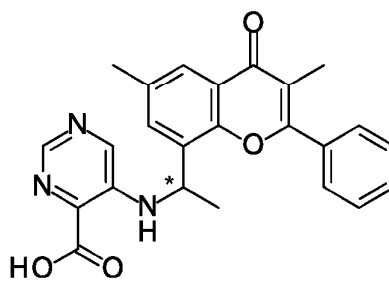
- 274 -



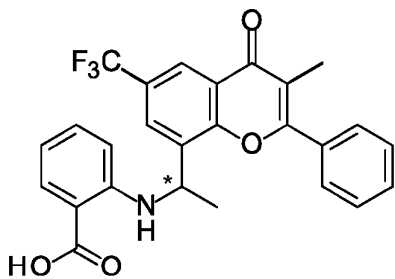
- 277 -



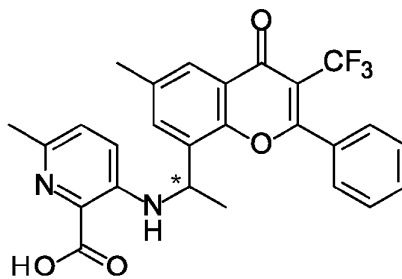
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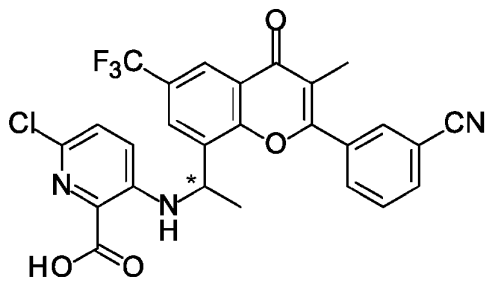
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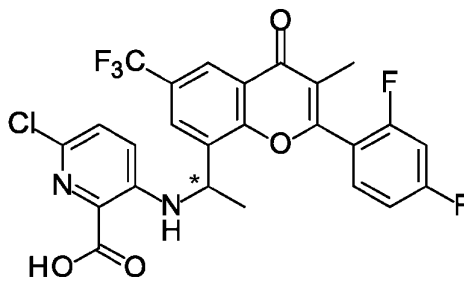
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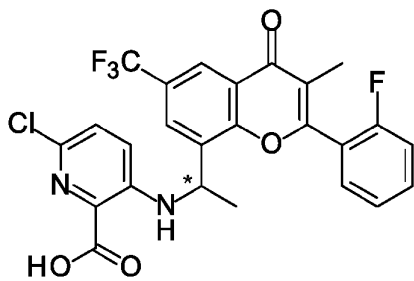
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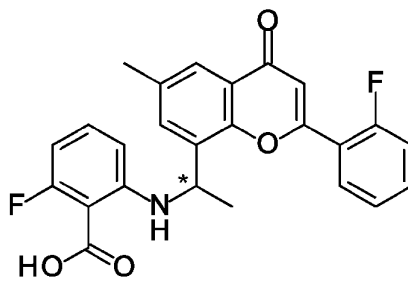
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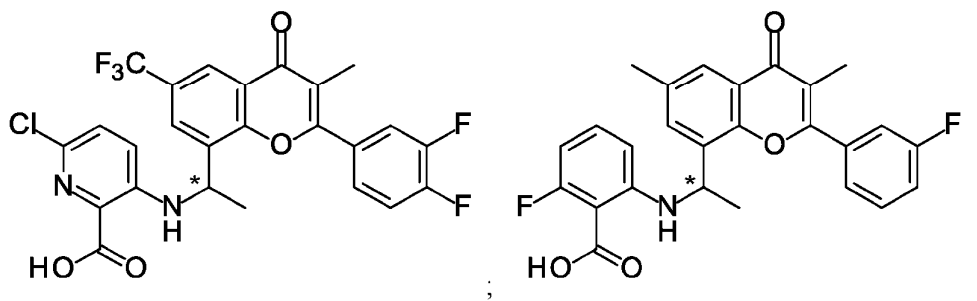
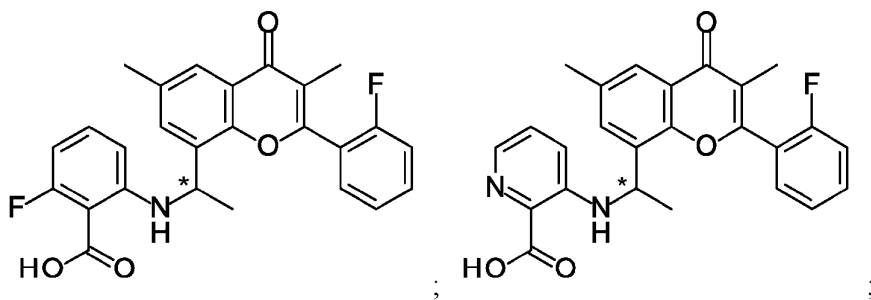
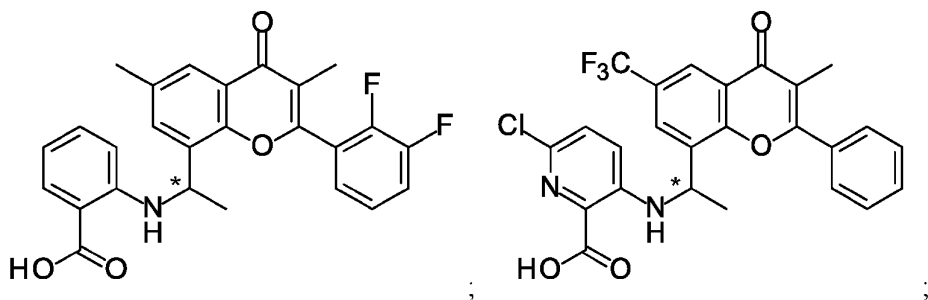
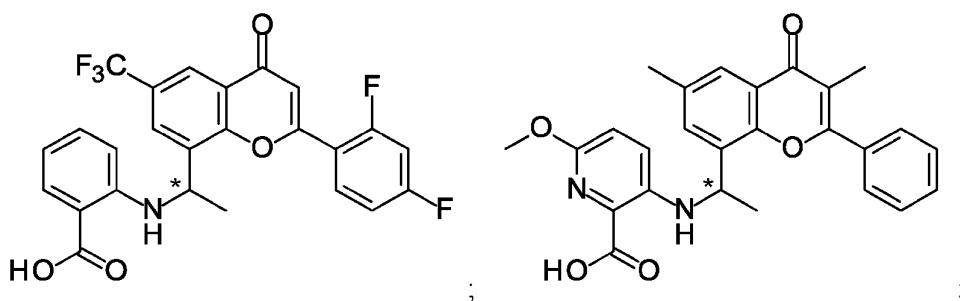


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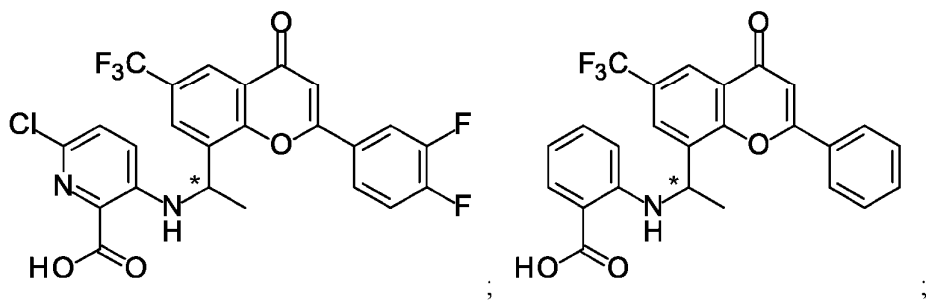
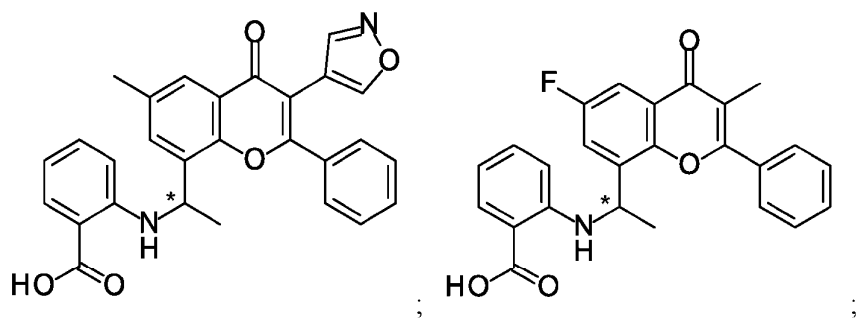
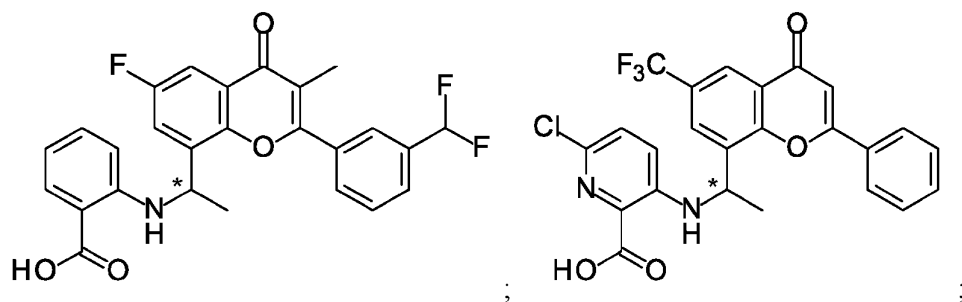
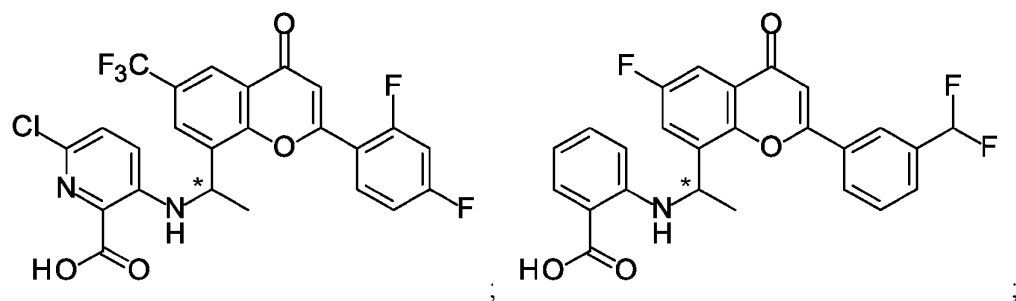


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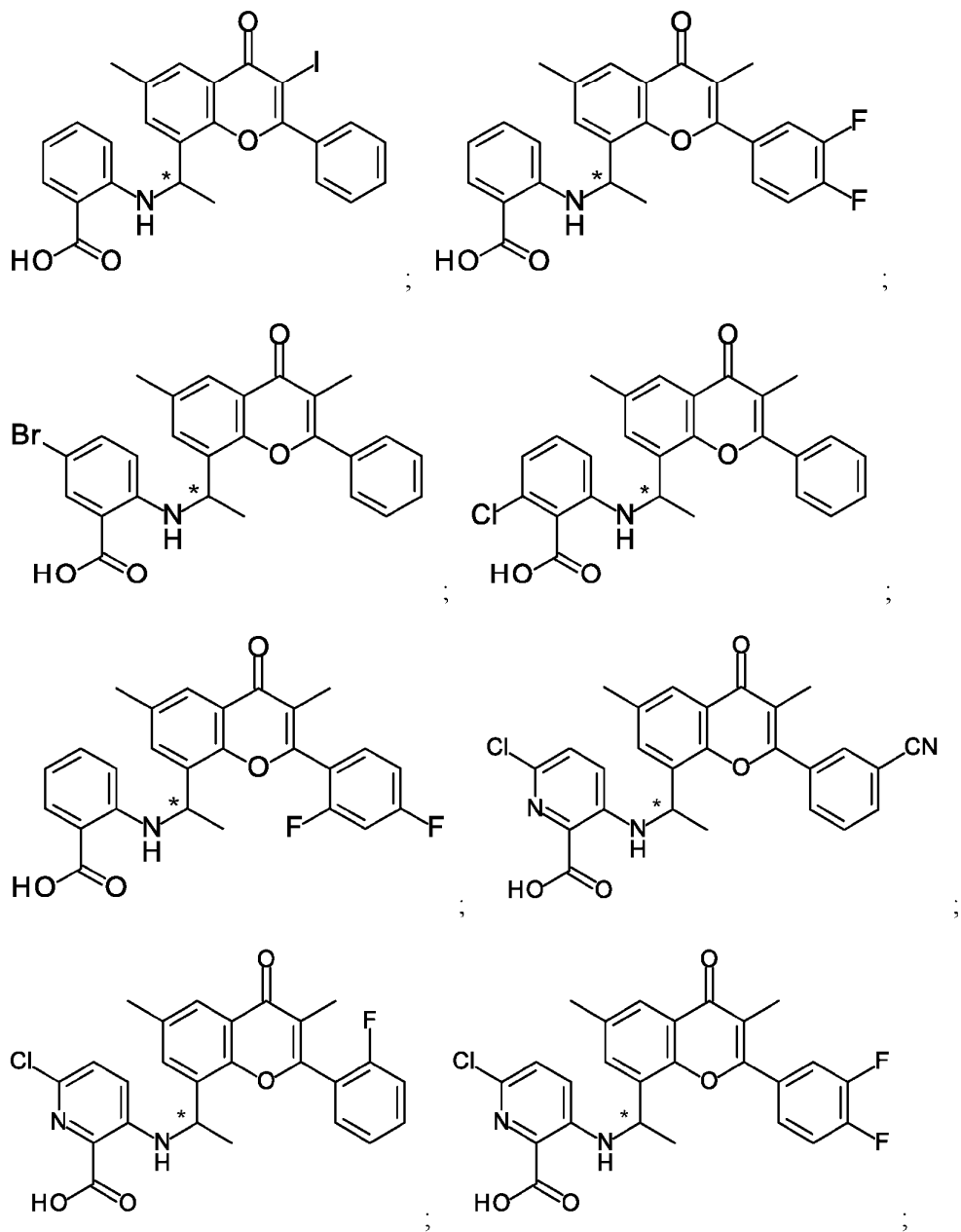
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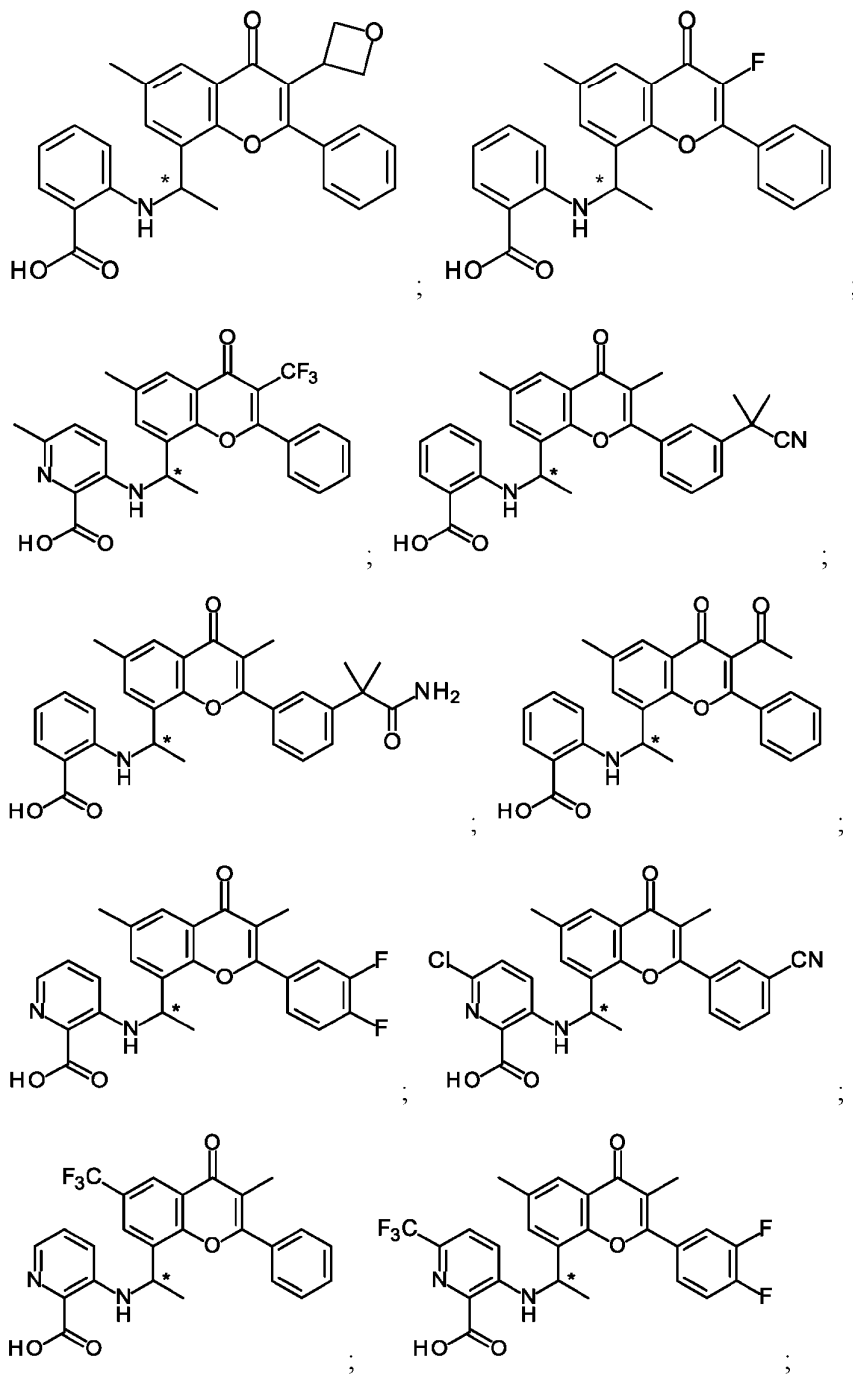
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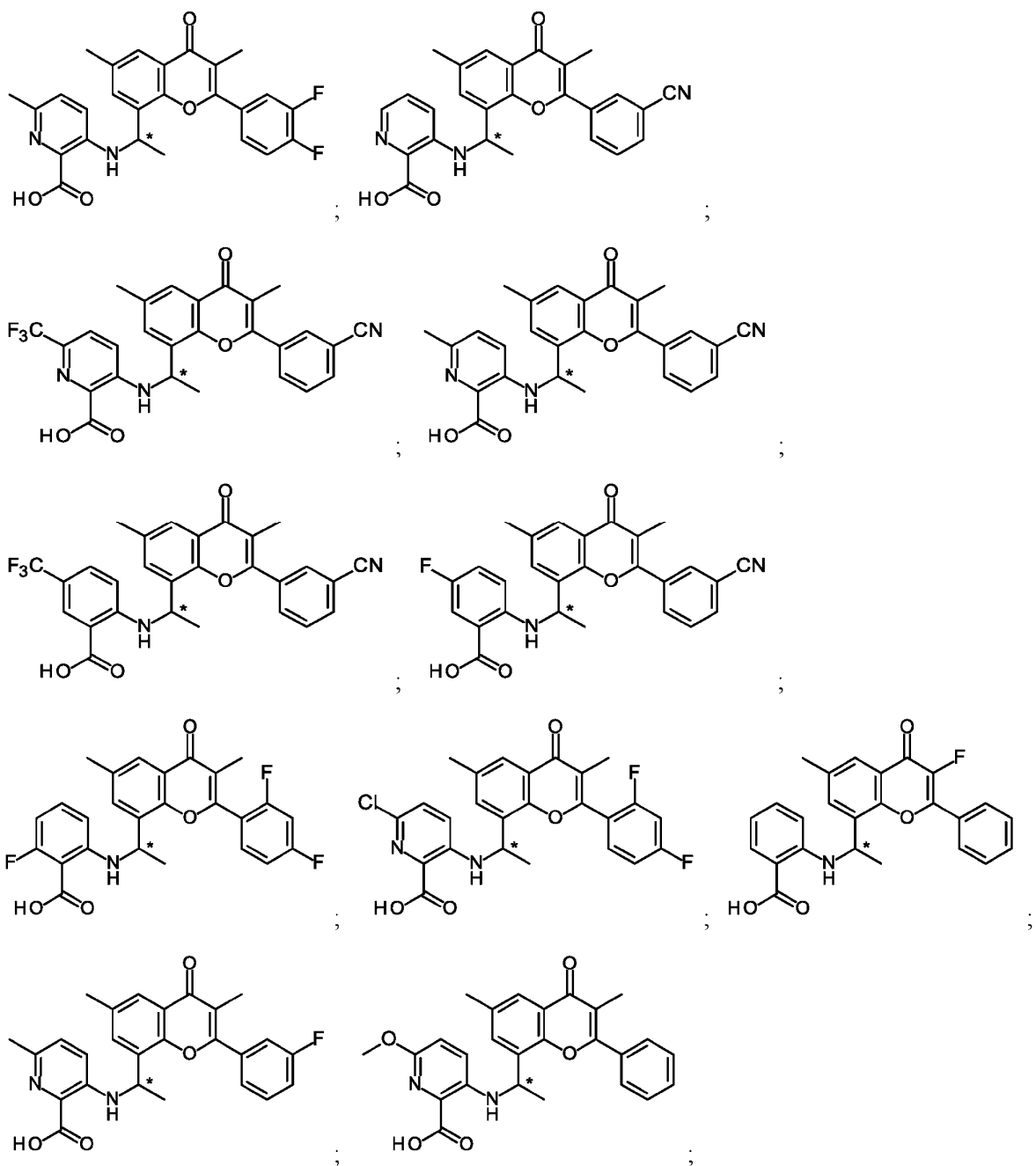
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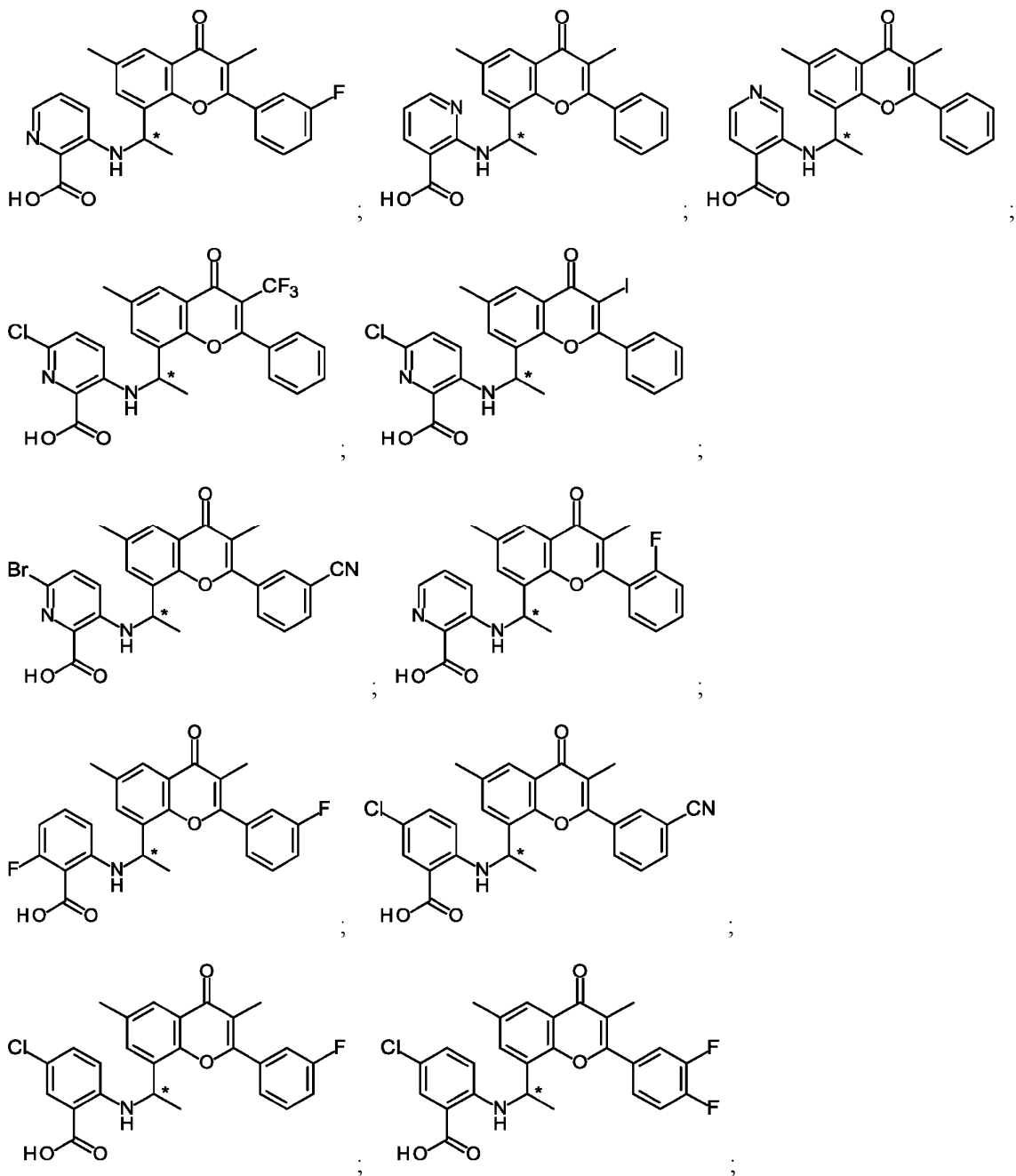
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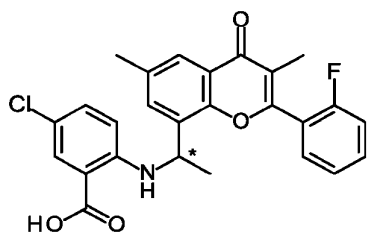
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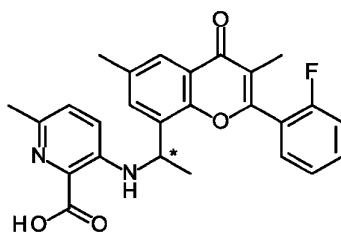
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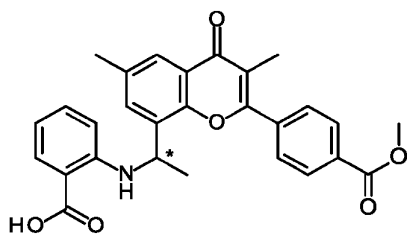
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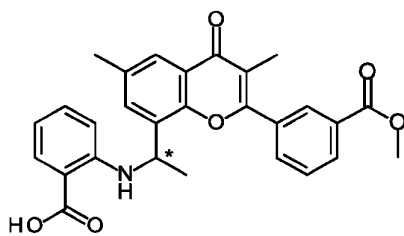
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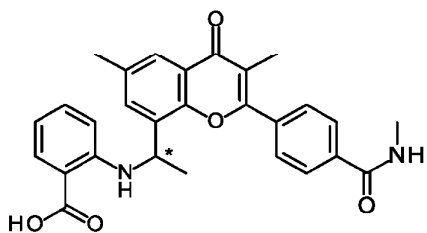
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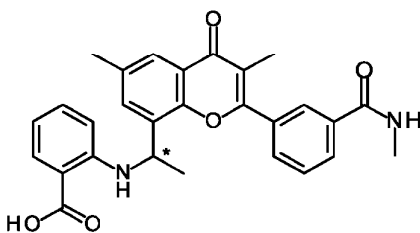
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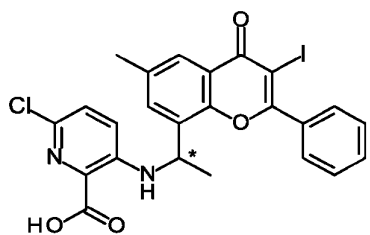
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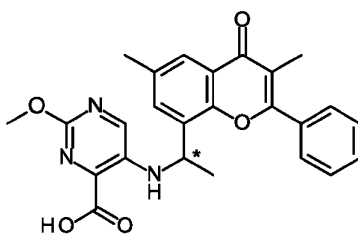
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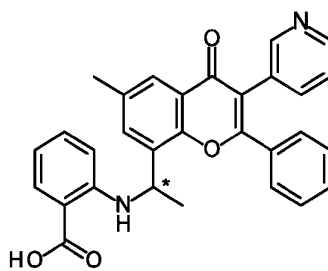
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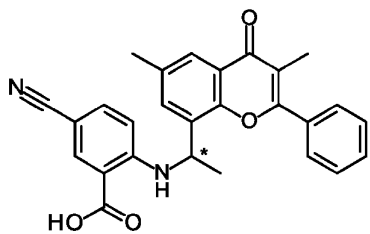
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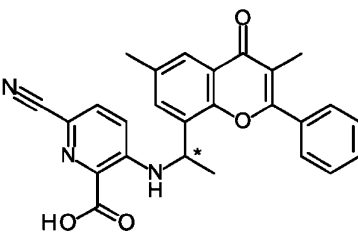
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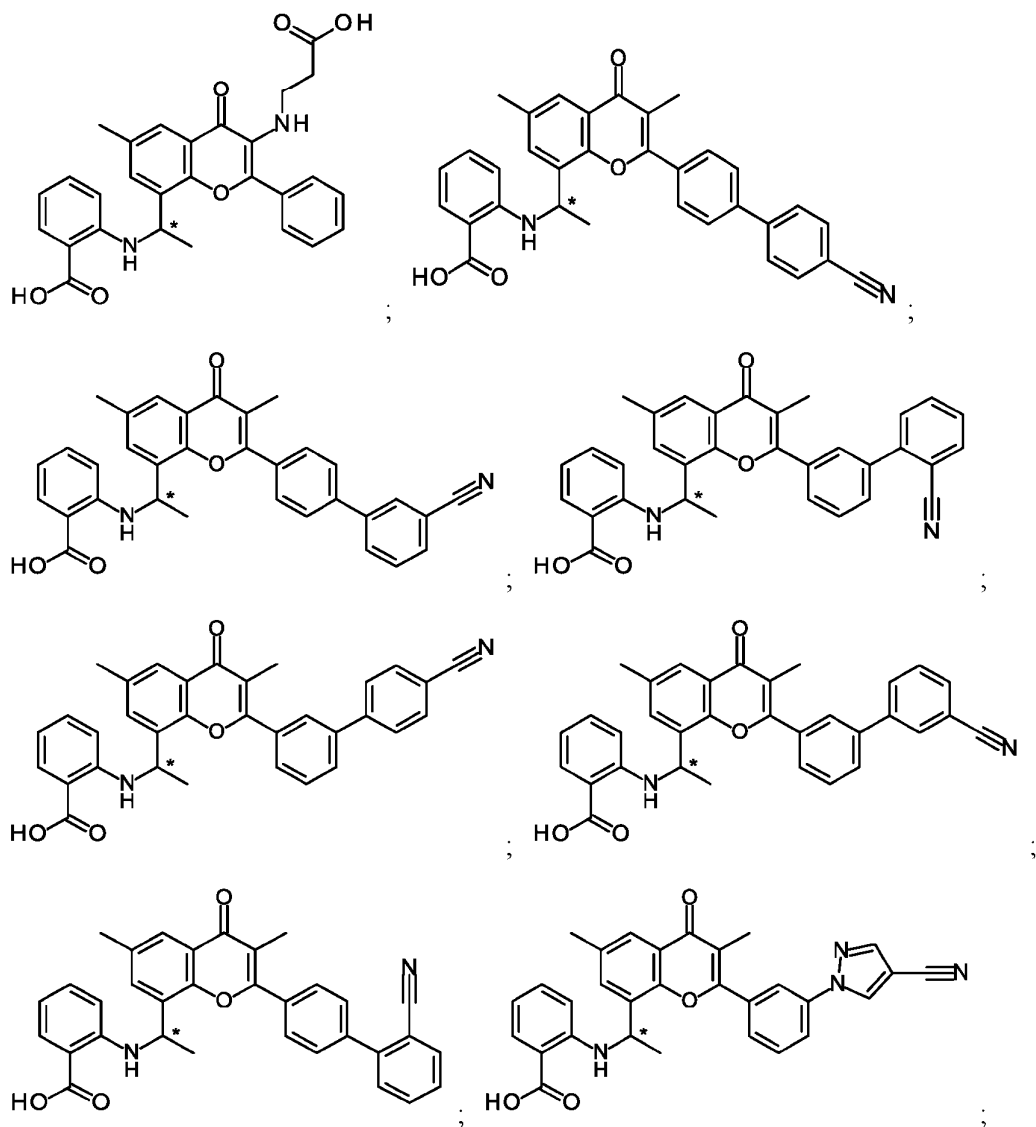


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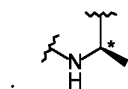


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or a pharmaceutically acceptable salt thereof. In yet a further embodiment, the bond at the * position



is . In yet a further embodiment, the bond at the * position is



[593] A pharmaceutically acceptable salt of a compound of the present invention is, for example, an acid-addition salt of a compound of the invention, which is sufficiently basic, for example, an acid-

addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric, methane sulfonate or maleic acid. In addition, a pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, diethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. Pharmaceutically acceptable salts, and common methodology for preparing them are well known in the art (*see, e.g., P. Stahl, et al. Handbook of Pharmaceutical Salts: Properties, Selection, and Use, 2nd Revised Edition (Wiley-VCH, 2011); S.M. Berge, et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66, No. 1, January 1977*).

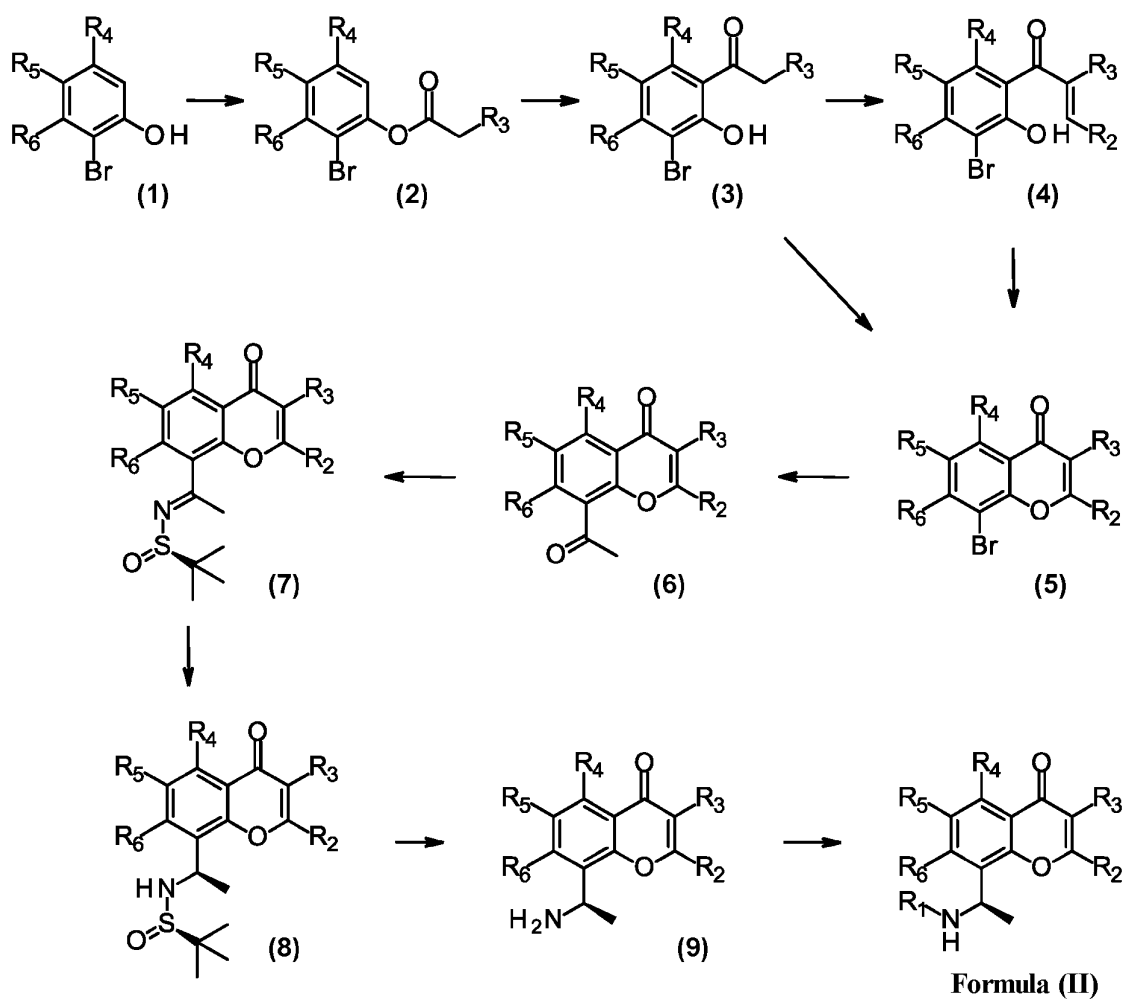
[594] Further representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble, and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulanate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate, pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[595] The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the

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present invention can be synthesized by following the steps outlined in General Schemes 1, 2, 3, and 4 which comprise different sequences of assembling intermediates or compounds. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated below.

Scheme 1



[596] Scheme 1 depicts the preparation of compounds of Formula (II), where R is H and R_7 is methyl. Acylation of substituted phenol (1) may provide ester (2). Ester (2) may undergo rearrangement under Lewis acid (e.g., $AlCl_3$) or Brønsted acid (e.g., triflic acid) conditions to the

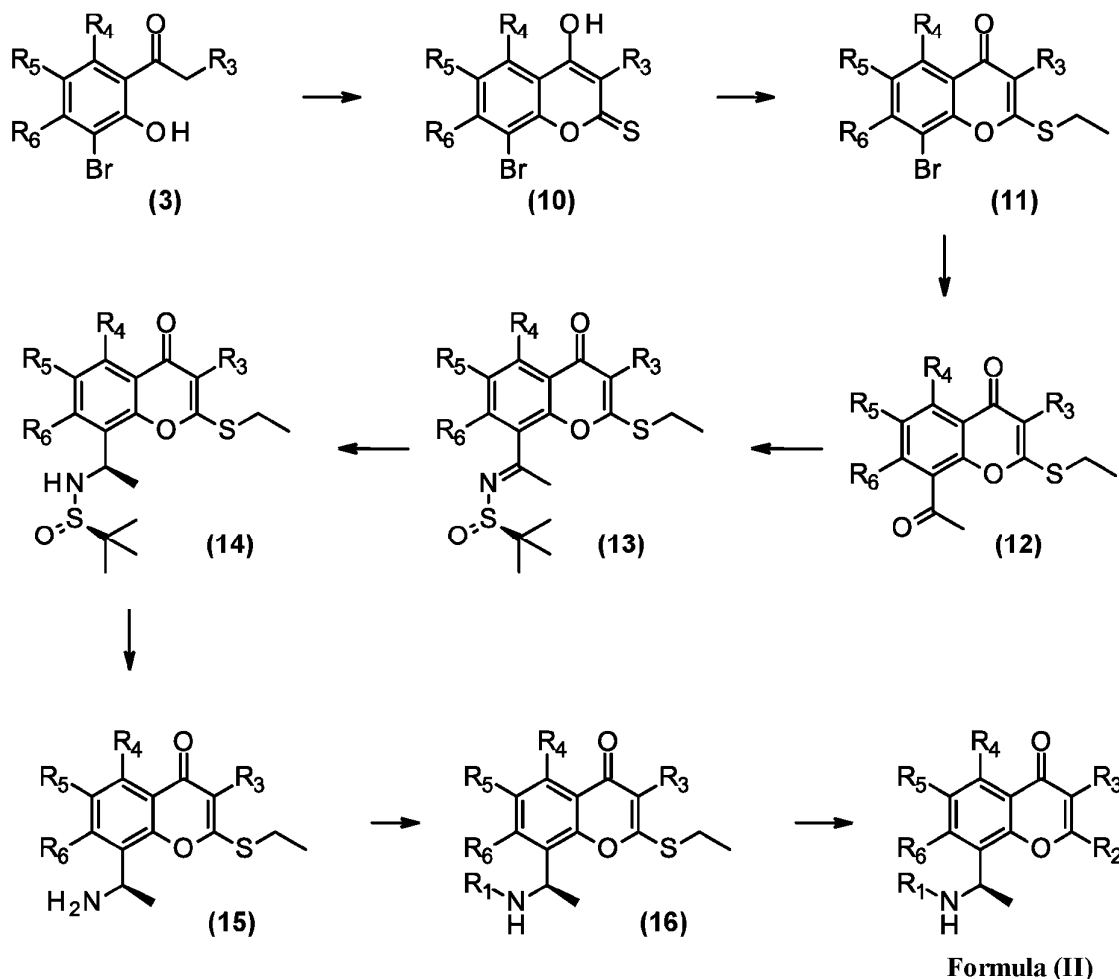
hydroxy aryl ketone (3). Acidic condensation of an aryl aldehyde with hydroxy aryl ketone (3) may provide keto-alkene (4) which may cyclize to the 2-substituted chromen-4-one (5). Alternatively, alkylation of hydroxy aryl ketone (3) with an aryl halide in the presence of a base (e.g., pyridine or lithium bis(trimethylsilyl)amide), followed by acidic conditions (e.g., HCl) may affect cyclization to 2-substituted chromen-4-one (5).

[597] Phenyl bromide (5) can be acylated via palladium catalysis to produce acyl chromen-4-one (6). Exemplary palladium catalysis conditions may include phenyl bromide (5), about 5-10 mol% $\text{PdCl}_2(\text{Ph}_3)_2$ and about 1.2 mol% tributyl(1-ethoxyvinyl)stannane in about 30-35 equivalents dioxane at 95°C for about 16 hours; or phenyl bromide (5), about 1 mol% $\text{Pd}(\text{OAc})_2$, about 2 mol% 1,3-bis(diphenylphosphino)propane, about 5 equivalents butyl vinyl ether, about 3 equivalents triethylamine, and about 10 volumes of ethylene glycol at about 100°C for about 16 hours.

Condensation of ketone (6) with tert-butanefulfinamide using a Lewis acidic dehydrating agent such as a titanium(IV) alkoxide may afford ketimine (7). Asymmetric reduction of sulfinimine (7) may be affected with a borohydride reagent in the presence of a transition metal catalyst such as cerium (III) chloride to yield chirally enriched sulfinamide (8). Removal of the sulfinyl group under acidic conditions may be used to transform sulfinamide (8) to benzylamine (9) which can be alkylated with an aryl or heteroaryl halide under Finkelstein or Ullmann-type conditions to give compounds of Formula (II) after hydrolysis of ester present on R_1 .

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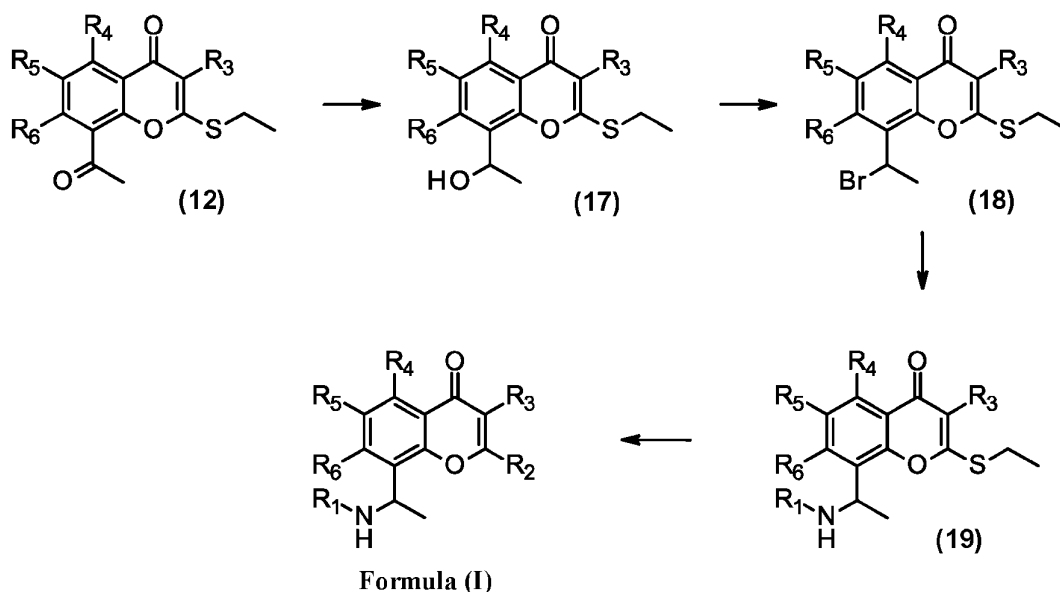
Scheme 2



[598] Scheme 2 depicts additional preparation of compounds of Formula (II), where **R** is H and **R₇** is methyl. Basic deprotonation of ketone (3) in the presence of carbon disulfide gives the bicyclic chromene-2-thione (10). Alkylation of thione (10) under basic conditions affords thioether (11). [599] Phenyl bromide (11) can be acylated via palladium catalysis to produce acyl chromen-4-one (12) which can be condensed with tert-butanesulfinamide using a Lewis acidic dehydrating agent such as a titanium(IV) alkoxide to afford ketimine (13). Asymmetric reduction of sulfinimine (13) may be affected with a borohydride reagent in the presence of a transition metal catalyst such as

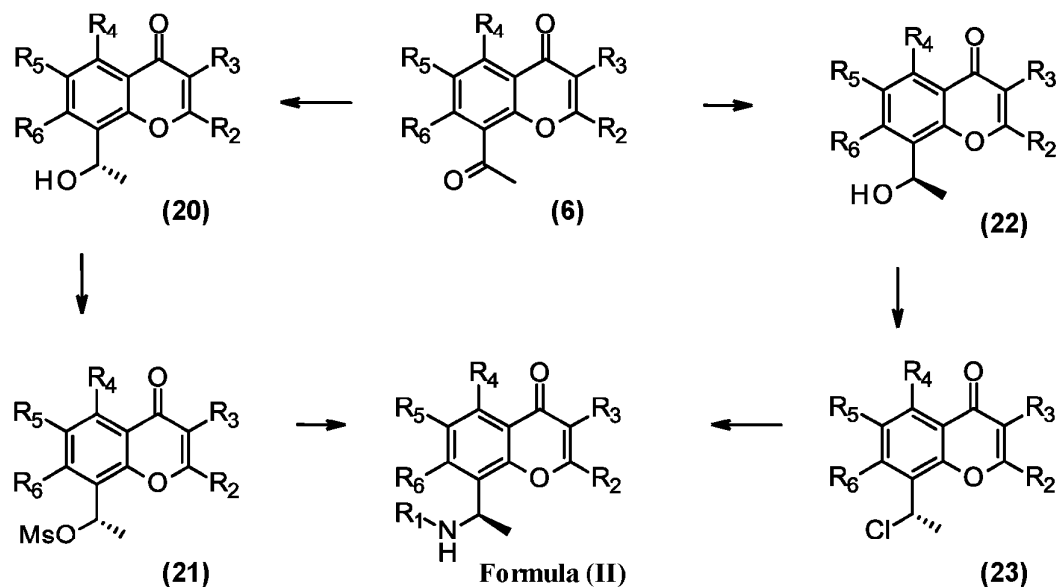
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cerium (III) chloride to yield chirally enriched sulfinamide (14). Removal of the sulfinyl group under acidic conditions may be used to transform sulfinamide (14) to benzylamine (15) which can be alkylated with an aryl or heteroaryl halide under Finkelstein or Ullmann-type conditions to give arylamine (16). Thiolether (16) can be converted to compounds of Formula (II) using transition metal catalysis to couple phenyl boronic acids, boronic esters, or other coupling partners, followed by hydrolysis of ester present on R₁.

Scheme 3

[600] Scheme 3 depicts the preparation of compounds of Formula (I), where **R** is H, **R₇** is methyl, and **R₈** is H. Aryl ketone (12) can be reduced to hydroxy compound (17) with a reagent such as sodium borohydride. Use of a halogenating agent such as phosphorus tribromide can be used to convert hydroxy compound (17) to the halo compound (18). Halo compound (18) can be used to alkylate an arylamine or heteroarylamine to give arylamine or heteroarylamine (19). Thiolether (19) can be converted to compounds of Formula (I) using transition metal catalysis to couple phenyl boronic acids, boronic esters, or other coupling partners, followed by hydrolysis of ester present on R₁.

Scheme 4



[601] Scheme 4 depicts the preparation of compounds of Formula (II) where **R** is H and **R**₇ is methyl. Ketone (6) can be reduced to hydroxy compound (20) with a chiral catalyst such as the Noyori catalyst. The hydroxyl compound (20) can be converted into a leaving group with methanesulfonic anhydride or methanesulfonyl chloride to give mesylate (21). Mesylate (21) can be used to alkylate an arylamine or heteroarylamine to give compounds of Formula (II) after hydrolysis of the ester present on R₁.

[602] Alternatively, ketone (6) can be reduced to hydroxy compound (22) with a chiral catalyst such as the Noyori catalyst. The hydroxyl group can be converted to chloride (23) with a chlorinating agent such as 2,4,6-trichloro-1,3,5-triazine. Chloride (23) can then be used to alkylate an arylamine or heteroarylamine to give compounds of Formula (II) after hydrolysis of the ester present on R₁.

Pharmaceutical Compositions

[603] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I), (II), or (III) as an active ingredient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I), (II), or

(III), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

[604] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[605] The compounds of Formula (I), (II), or (III) can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of Formula (I), (II), or (III) can also be formulated for intravenous (bolus or in-fusion), intraperitoneal, topical, subcutaneous, intramuscular or transdermal (*e.g.*, patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[606] The formulation of the present disclosure may be in the form of an aqueous solution comprising an aqueous vehicle. The aqueous vehicle component may comprise water and at least one pharmaceutically acceptable excipient. Suitable acceptable excipients include those selected from the group consisting of a solubility enhancing agent, chelating agent, preservative, tonicity agent, viscosity/suspending agent, buffer, and pH modifying agent, and a mixture thereof.

[607] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound any one of the Formulae disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[608] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[609] The compositions of the disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

Methods of Use

[610] In some aspects, the present disclosure provides a method of modulating PI3K (e.g., PI3K α) activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof.

[611] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[612] In some aspects, the present disclosure provides a method of treating a disease or disorder disclosed herein in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[613] In some embodiments, the disease or disorder is associated with an implicated PI3K activity. In some embodiments, the disease or disorder is a disease or disorder in which PI3K activity is implicated.

[614] In some embodiments, the disease or disorder is a cancer.

[615] In some embodiments, the cancer is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, aids-related cancers, aids-related lymphoma, anal cancer, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain tumors, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, cancer of unknown primary, cardiac (heart) tumors, atypical teratoid/rhabdoid tumor, primary CNS lymphoma, cervical cancer, cholangiocarcinoma, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer,

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craniopharyngioma, cutaneous t-cell lymphoma, mycosis fungoides, Sézary syndrome, ductal carcinoma in situ (DCIS), embryonal tumors, medulloblastoma, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, fallopian tube cancer, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, malignant gastrointestinal stromal tumors (GIST), germ cell tumors, gestational trophoblastic disease, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Langerhans cell histiocytosis, Hodgkin lymphoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, male breast cancer, intraocular melanoma, Merkel cell carcinoma, malignant mesothelioma, metastatic cancer, metastatic squamous neck cancer, midline tract carcinoma with nut gene changes, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasms, myelodysplastic syndromes, myelodysplastic neoplasms, myeloproliferative neoplasms, chronic myeloproliferative neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, lip and oral cavity cancer, oropharyngeal cancer, malignant fibrous histiocytoma of bone, ovarian cancer, pancreatic cancer, pancreatic neuroendocrine tumors (islet cell tumors), papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, plasma cell neoplasm, multiple myeloma, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, recurrent cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, childhood vascular tumors, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma of the skin, testicular cancer, oropharyngeal cancer, hypopharyngeal cancer, thymoma, thymic carcinoma, thyroid cancer, tracheobronchial tumors, transitional cell cancer of the renal pelvis and ureter, urethral cancer, uterine sarcoma, vaginal cancer, vascular tumors, vulvar cancer, and Wilms tumor.

[616] In some embodiments, the cancer is Endometrial cancer, Breast cancer, Oesophageal squamous-cell cancer, Cervical squamous-cell carcinoma, Cervical adenocarcinoma, Colorectal

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adenocarcinoma, Bladder Urothelial Carcinoma, Glioblastoma, Ovarian cancer, Non-small-cell Lung cancer, Esophagogastric cancer, Nerve-sheath tumor, Head and neck squamous-cell carcinoma, Melanoma, Esophagogastric adenocarcinoma, Soft-tissue sarcoma, Prostate cancer, Fibrolamellar carcinoma, Hepatocellular carcinoma, Diffuse glioma, Colorectal cancer, Pancreatic cancer, Cholangiocarcinoma, B-cell lymphoma, Mesothelioma, Adrenocortical carcinoma, Renal non-clear-cell carcinoma, Renal clear-cell carcinoma, Germ-cell carcinoma, Thymic tumor, Pheochromocytoma, Miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, or encapsulated glioma.

[617] In some embodiments, the cancer is a breast cancer, a prostate cancer, or a brain cancer.

[618] In some embodiments, the cancer is a breast cancer. In some embodiments, the cancer is a prostate cancer. In some embodiments, the cancer is a brain cancer.

[619] In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is ductal carcinoma in situ (DCIS). In some embodiments, the breast cancer is invasive ductal carcinoma. In some embodiments, the breast cancer is triple negative breast cancer. In some embodiments, the breast cancer is medullary carcinoma. In some embodiments, the breast cancer is tubular carcinoma. In some embodiments, the breast cancer is mucinous carcinoma. In some embodiments, the breast cancer is Paget disease of the breast or nipple. In some embodiments, the breast cancer is inflammatory breast cancer (IBC). In some embodiments, the breast cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

[620] In some embodiments, the prostate cancer is an adenocarcinoma. In some embodiments, the prostate cancer is a small cell carcinoma. In some embodiments, the prostate cancer is a neuroendocrine tumor. In some embodiments, the prostate cancer is a transitional cell carcinoma. In some embodiments, the prostate cancer is a sarcoma.

[621] In some embodiments, the brain cancer is an acoustic neuroma. In some embodiments, the brain cancer is an astrocytoma. In some embodiments, the brain cancer is a brain metastasis. In some embodiments, the brain cancer is choroid plexus carcinoma. In some embodiments, the brain cancer is craniopharyngioma. In some embodiments, the brain cancer is an embryonal tumor. In some

embodiments, the brain cancer is an ependymoma. In some embodiments, the brain cancer is a glioblastoma. In some embodiments, the brain cancer is a glioma. In some embodiments, the brain cancer is a medulloblastoma. In some embodiments, the brain cancer is a meningioma. In some embodiments, the brain cancer is an oligodendroglioma. In some embodiments, the brain cancer is a pediatric brain tumor. In some embodiments, the brain cancer is a pineoblastoma. In some embodiments, the brain cancer is a pituitary tumor.

[622] In some embodiments, the disease or disorder associated with PI3K includes, but is not limited to, CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

[623] In some embodiments, the diseases or disorder associated with PI3K is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome).

[624] In some embodiments, the disease or disorder associated with PI3K is PIK3CA-related overgrowth syndrome (PROS).

[625] In some embodiments, the disease or disorder associated with PI3K is breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

[626] In some embodiments, the disease or disorder associated with PI3K is a breast neoplasm, a thyroid neoplasm, an ovarian neoplasm, non-small-cell lung carcinoma, an endometrial neoplasm, or a pancreatic neoplasm. In some embodiments, the disease or disorder associated with PI3K is a breast neoplasm. In some embodiments, the disease or disorder associated with PI3K is a thyroid neoplasm. In some embodiments, the disease or disorder associated with PI3K is an ovarian neoplasm. In some embodiments, the disease or disorder associated with PI3K is non-small-cell lung carcinoma. In some embodiments, the disease or disorder associated with PI3K is an endometrial neoplasm. In some embodiments, the disease or disorder associated with PI3K is a pancreatic neoplasm.

[627] In some embodiments, the disease or disorder associated with PI3K is breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

[628] In some embodiments, the disease or disorder associated with PI3K is leukemia, lymphoma, or sarcoma.

[629] In some embodiments, the cancer is endometrial cancer, head and neck cancer, or a sarcoma.

[630] In some embodiments, the cancer is endometrial cancer. In some embodiments the cancer is head and neck cancer. In some embodiments, the cancer is a sarcoma.

[631] In some embodiments, the sarcoma is soft tissue sarcoma, osteosarcoma, chondrosarcoma, Ewing sarcoma, hemangioendothelioma, angiosarcoma, fibrosarcoma, myofibrosarcoma, chordoma, adamantinoma, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, synovial sarcoma, or malignant solitary fibrous tumor.

[632] In some embodiments, the sarcoma is soft tissue sarcoma. In some embodiments the soft tissue sarcoma is liposarcoma, atypical lipomatous tumor, dermatofibrosarcoma protuberans, malignant solitary fibrous tumor, inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma, fibrosarcoma, myxofibrosarcoma, low-grade fibromyxoid sarcoma, giant cell tumor of soft tissues, leiomyosarcoma, malignant glomus tumor, rhabdomyosarcoma, hemangioendothelioma, angiosarcoma of soft tissue, extraskeletal osteosarcoma, gastrointestinal stromal tumor, malignant gastrointestinal stromal tumor (GIST), malignant peripheral nerve sheath tumor, malignant Triton tumor, malignant granular cell tumor, malignant ossifying fibromyxoid tumor, stromal sarcoma, myoepithelial carcinoma, malignant phosphaturic mesenchymal tumor, synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft tissue, extraskeletal myxoid chondrosarcoma, extraskeletal Ewing sarcoma, desmoplastic small round cell tumor, extrarenal rhabdoid tumor, perivascular epithelioid cell tumor, intimal sarcoma, undifferentiated spindle cell sarcoma, undifferentiated pleomorphic sarcoma, undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma, or undifferentiated sarcoma, not otherwise specified.

[633] In some aspects, the present disclosure provides a method of treating or preventing a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount

of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[634] In some aspects, the present disclosure provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[635] In some aspects, the present disclosure provides a method of treating or preventing a breast cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[636] In some aspects, the present disclosure provides a method of treating a breast cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[637] In some aspects, the present disclosure provides a method of treating or preventing a prostate cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[638] In some aspects, the present disclosure provides a method of treating a prostate cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[639] In some aspects, the present disclosure provides a method of treating or preventing a brain cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[640] In some aspects, the present disclosure provides a method of treating a brain cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of

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a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[641] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in therapy.

[642] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in modulating PI3K (e.g., PI3K α) activity (e.g., *in vitro* or *in vivo*).

[643] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[644] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder disclosed herein.

[645] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating or preventing a cancer.

[646] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating a cancer.

[647] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating or preventing a breast cancer.

[648] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating a breast cancer.

[649] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating or preventing a prostate cancer.

[650] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating a prostate cancer.

[651] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating or preventing a brain cancer.

[652] In some aspects, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in treating a brain cancer.

[653] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for modulating PI3K (e.g., PI3K α) activity (e.g., *in vitro* or *in vivo*).

[654] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[655] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or disorder disclosed herein.

[656] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a cancer in a patient in need thereof.

[657] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cancer in a patient in need thereof.

[658] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a breast cancer in a patient in need thereof.

[659] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a breast cancer in a patient in need thereof.

[660] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a prostate cancer in a patient in need thereof.

[661] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a prostate cancer in a patient in need thereof.

[662] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or

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(III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a brain cancer in a patient in need thereof.

[663] In some aspects, the present disclosure provides use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a brain cancer in a patient in need thereof.

[664] The present disclosure provides compounds that function as modulators of PI3K activity. The present disclosure therefore provides a method of modulating PI3K activity *in vitro* or *in vivo*, said method comprising contacting a cell with a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[665] In some embodiments, PI3K modulation is inhibition of PI3K.

[666] In some embodiments, the PI3K inhibitor is a PI3K α inhibitor. In some embodiments, the PI3K inhibitor is a PI3K α H1047R mutant inhibitor.

[667] Effectiveness of compounds of the disclosure can be determined by industry-accepted assays/ disease models according to standard practices of elucidating the same as described in the art and are found in the current general knowledge.

[668] The present disclosure also provides a method of treating a disease or disorder in which PI3K activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

Routes of Administration

[669] The compounds of Formula (I), (II), or (III), or pharmaceutical compositions comprising these compounds may be administered to a patient by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[670] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal

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(e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

EXAMPLES

[671] Exemplary compounds of Formula (I), (II), and (III) are synthesized and tested in the examples. It is understood that compounds of Formula (I), (II), and (III) may be converted to the corresponding pharmaceutically acceptable salts of the compounds using routine techniques in the art (e.g., by saponification of an ester to the carboxylic acid salt, or by hydrolyzing an amide to form a corresponding carboxylic acid and then converting the carboxylic acid to a carboxylic acid salt).

[672] Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 300 MHz as stated and at 300.3 K unless otherwise stated; the chemical shifts (δ) are reported in parts per million (ppm). Spectra were recorded using a Bruker or Varian instrument with 8, 16 or 32 scans.

[673] LC-MS chromatograms and spectra were recorded using an Agilent 1200 or Shimadzu LC-20 AD&MS 2020 instrument using a C-18 column such as a Luna-C18 2.0x30 mm or Xbridge Shield RPC18 2.1x50 mm. Injection volumes were 0.7 – 8.0 μ l and the flow rates were typically 0.8 or 1.2 ml/min. Detection methods were diode array (DAD) or evaporative light scattering (ELSD) as well as positive ion electrospray ionization. MS range was 100 - 1000 Da. Solvents were gradients of water and acetonitrile both containing a modifier (typically 0.01 – 0.04 %) such as trifluoroacetic acid or ammonium carbonate.

[674] Abbreviations:

AcOH / HOAc	Acetic Acid
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate

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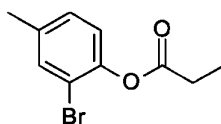
CDCl ₃	Chloroform- <i>d</i>
DCM	Dichloromethane
DIEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DMSO- <i>d</i> ₆	Hexadeuterodimethylsulfoxide
eq.	equivalents
EtI	Ethyl iodide
EtOAc	ethyl acetate
h	hour(s)
HEPES	4- (2-hydroxyethyl)-1-piperazineethanesulfonic acid
¹ H NMR	Proton nuclear magnetic resonance spectroscopy
LC-MS	Liquid chromatography-mass spectrometry
MeOH	Methanol
min	minute(s)
NaHMDS	Sodium bis(trimethylsilyl)amide
PIP2	Phosphatidylinositol 4,5-bisphosphate
PPh ₃	triphenylphosphine
ppm	parts per million
rt	room temperature
TFA	trifluoroacetic acid

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THF Tetrahydrofuran

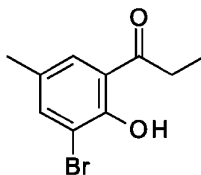
Ti(i-PrO)₄ Titanium(IV) isopropoxide

[675] Intermediate 1: (2-Bromo-4-methyl-phenyl) propanoate



[676] A mixture of 2-bromo-4-methyl-phenol (10.0 g, 53.5 mmol) and pyridine (6.34 g, 80.2 mmol) in DCM (100 mL) was treated with propanoyl chloride (5.44 g, 58.8 mmol) at 0°C and stirred at 25°C for 16 h. The mixture was diluted with water (100 mL), the pH adjusted to 5 with HCl (2 M), and extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as an oil (13 g, crude). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.17 (t, J=7.6 Hz, 3 H), 2.30 (s, 3 H), 2.62 (q, J=7.6 Hz, 2 H), 7.11-7.18 (m, 1 H), 7.19-7.26 (m, 1 H), 7.50-7.55 (m, 1 H).

[677] Intermediate 2: 1-(3-Bromo-2-hydroxy-5-methyl-phenyl)propan-1-one

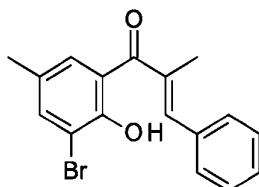


[678] A mixture of (2-bromo-4-methyl-phenyl) propanoate (12.5 g, 51.4 mmol) and AlCl₃ (24.0 g, 180 mmol) was stirred at 140°C for 1 h. When cooled to rt, the mixture was quenched with water (80 mL) dropwise and stirred for 30 min. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated and triturated with petroleum ether (20 mL) to give the product as a solid (9.82 g, 79%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.10 (t, J=7.2 Hz, 3 H), 2.28 (s, 3 H), 3.15 (q, J=7.2 Hz, 2 H), 7.66-7.73 (m, 1 H), 7.77-7.83 (m, 1 H), 12.66 (s, 1 H).

[679] Intermediate 3: (E)-1-(3-Bromo-2-hydroxy-5-methyl-phenyl)-2-methyl-3-phenyl-prop-2-en-1-

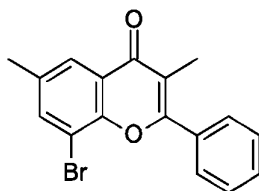
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one



[680] A mixture of 1-(3-bromo-2-hydroxy-5-methyl-phenyl)propan-1-one (200 g, 822.72 mmol), benzaldehyde (96.04 g, 904.99 mmol), AcOH (105.23 g, 1.75 mol), and piperidine (172.33 g, 2.02 mol) in EtOH (1600 mL) was stirred at 70°C for 16 h. The resulting dark solution was poured into water (3 L), filtered, and the solid dissolved in 6 L of DCM. The organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as a dark gum. MS ES+ *m/z* 331, 333 [M+H]⁺.

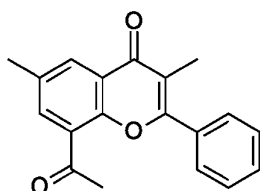
[681] Intermediate 4: 8-Bromo-3,6-dimethyl-2-phenyl-chromen-4-one



[682] A mixture of (E)-1-(3-bromo-2-hydroxy-5-methyl-phenyl)-2-methyl-3-phenyl-prop-2-en-1-one (284 g, 857.48 mmol) and I₂ (21.76 g, 85.75 mmol, 17.27 mL, 0.1 eq) in DMSO (1200 mL) was stirred at 140°C for 2 h to give a black-brown solution. Cooled to rt, poured the reaction into 3 L of water, filtered, dissolved the solid product in DCM (4 L), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (1:1, 1 L) to give the product as a light yellow solid (195 g, 69%). MS ES+ *m/z* 329, 331 [M+H]⁺.

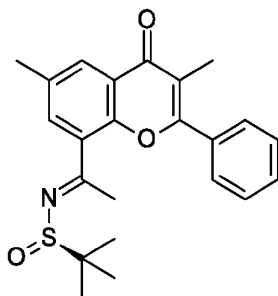
[683] Intermediate 5: 8-Acetyl-3,6-dimethyl-2-phenyl-chromen-4-one

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[684] A mixture of 8-bromo-3,6-dimethyl-2-phenyl-chromen-4-one (195 g, 592.37 mmol), bis(triphenylphosphine)palladium(II) dichloride (20.79 g, 29.62 mmol), and tributyl(1-ethoxyvinyl)stannane (256.72 g, 710.84 mmol, 239.92 mL) in dioxane (1600 mL) was stirred under N₂ at 95°C for 16 h to give a black-brown solution. After cooling to rt, treated the reaction with 1M aqueous HCl (100 mL) and stirred at 20°C for 30 min. The mixture was quenched with saturated aqueous KF (2000 mL), stirred for 30 min, and filtered. The filter cake was washed with 10% MeOH in DCM (5 x 5000 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (5/1, 1000 mL) to give a crude product which was triturated with DCM/MeOH (10/1, 500 mL) to give the product as a light yellow solid (180 g, 96%, 92% purity). MS ES+ *m/z* 293 [M+H]⁺.

[685] Intermediate 6: (NE,R)-N-[1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide

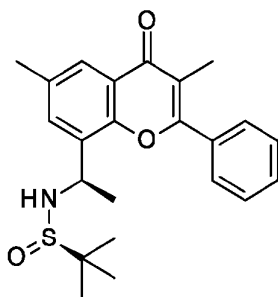


[686] To a mixture of 8-acetyl-3,6-dimethyl-2-phenyl-chromen-4-one (180 g, 615.75 mmol) and (R)-2-methylpropane-2-sulfinamide (149.26 g, 1.23 mol) in THF (1500 mL) was added tetraisopropoxytitanium (700.01 g, 2.46 mol, 726.90 mL). The mixture was stirred at 80°C for 56 h to give a black-brown solution. After cooling to rt, quenched the reaction with brine (2000 mL) and

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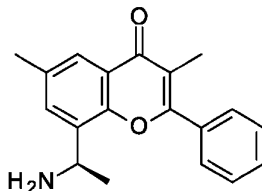
stirred for 30 min and filtered. The filter cake was washed with EtOAc (4000 mL). After separating the organic layer, the aqueous layer was extracted with EtOAc (1000 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (1/1, 600 mL) to give the product as a white solid (186 g, 76%). MS ES+ m/z 396 $[\text{M}+\text{H}]^+$.

[687] Intermediate 7: (R)-N-[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide



[688] To a mixture of (NE,R)-N-[1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide (186 g, 470.27 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (87.61 g, 235.14 mmol, 22.35 mL) in MeOH (1600 mL) was added NaBH_4 (26.69 g, 705.41 mmol) at 15°C. The mixture was stirred at 15°C for 1 h to give a dark suspension. The reaction was quenched with saturated aqueous NH_4Cl (1500 mL) at 15°C. Extracted with DCM (2 x 1500 mL), washed the combined organic phases with brine (1500 mL), dried the organic phase over anhydrous Na_2SO_4 , filtered, and concentrated to give the product as a yellow solid (180 g, 96%). MS ES+ m/z 398 $[\text{M}+\text{H}]^+$.

[689] Intermediate 8: 8-[(1R)-1-Aminoethyl]-3,6-dimethyl-2-phenyl-chromen-4-one

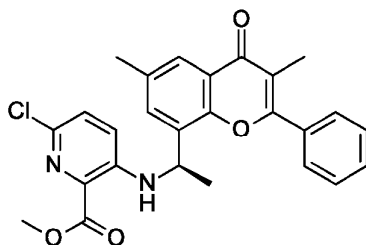


[690] A mixture of (R)-N-[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]-2-methyl-

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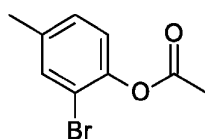
propane-2-sulfonamide (180 g, 452.80 mmol) in MeOH (1500 mL) was treated with HCl/MeOH (4 M, 300 mL) and the mixture was stirred at 15°C for 1 h to give a white suspension. Concentrated the reaction, poured the residue into water (1000 mL) and DCM (2000 mL), adjusted the pH to 12 with NH₃ in H₂O (25%), and extracted with DCM (2 x 1000 mL). The combined organic phases were washed with brine (1000 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was triturated with DCM (200 mL) to give the product as a white solid (122 g, 89%). MS ES+ *m/z* 294 [M+H]⁺.

[691] Intermediate 9: Methyl 6-chloro-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate



[692] A mixture of 8-[(1R)-1-aminoethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (10 g, 34.09 mmol), methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (7.75 g, 40.91 mmol) and DIEA (22.03 g, 170.44 mmol, 29.69 mL) in DMSO (100 mL) was stirred at 100°C for 16 h to give a dark solution. After cooling to rt, quenched the reaction with water (150 mL), extracted with EtOAc (2 x 300 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. Purified via silica gel using a gradient of EtOAc in petroleum ether (0 to 30%) to give the product as a yellow oil (15 g, 95%). MS ES+ *m/z* 463 [M+H]⁺.

[693] Intermediate 10: (2-Bromo-4-methyl-phenyl) acetate

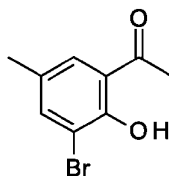


[694] A DCM (2.4 L) mixture of 2-bromo-4-methyl-phenol (300 g, 1.6 mol) and pyridine (152 g, 1.92 mol) at 0°C was treated with acetyl chloride and stirred at 25°C for 16 h. The mixture was

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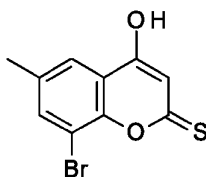
diluted with water (1500 mL), the pH adjusted to 5 with HCl (2 M aqueous), and extracted with DCM (3 X 500 mL). The combined organic extracts were washed with brine (2 x 250 mL), dried over Na₂SO₄, filtered, and concentrated to give the product as an oil (400 g, crude). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.24 (s, 3 H), 2.25 (s, 3 H), 6.91 (d, J=8.4 Hz, 2 H), 7.01-7.02 (m, 2 H), 7.33 (s, 1 H).

[695] Intermediate 11: 1-(3-Bromo-2-hydroxy-5-methyl-phenyl)ethanone



[696] A mixture of (2-bromo-4-methyl-phenyl) acetate (50 g, 218 mmol) and AlCl₃ (102 g, 764 mmol) was degassed and purged with N₂ three times and stirred at 140°C for 1 h. After cooling to rt, the reaction was diluted with DCM (30 mL) and dropped into 150 mL of water at 0°C. The mixture was filtered and the aqueous phase extracted with DCM (2 x 150 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was triturated with petroleum ether (2 x 150 mL) to give the product as a solid (30 g, 52%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H), 2.68 (s, 3 H), 7.73 (s, 1 H), 7.33 (s, 1 H), 12.64 (s, 1 H).

[697] Intermediate 12: 8-Bromo-4-hydroxy-6-methyl-chromene-2-thione

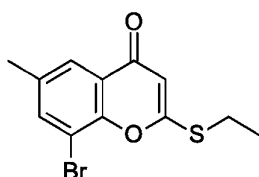


[698] A solution of 1-(3-bromo-2-hydroxy-5-methyl-phenyl)ethanone (65 g, 284 mmol) in THF (800 mL) was treated with NaHMDS (851 mL, 1 M) at -50°C over 30 min, allowed to warm to between -5°C and 0°C, and stirred for 1 h. The reaction was cooled to -20°C and treated with CS₂ (64.8 g, 851 mmol) dropwise over 1 h, allowed to warm to 25°C, and stirred for another 16 h. The

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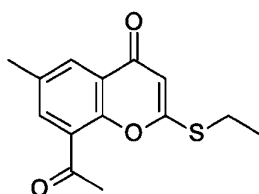
reaction was quenched with H₂SO₄ (800 mL, 15%) at -50°C over 1 h, allowed to warm to rt, and extracted with EtOAc (2 x 1L). The combined organic extracts were washed with brine (1L), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was triturated with EtOAc (0.5 L) to give the product as a solid (210 g crude, 64%, purity ~76%).

[699] Intermediate 13: 8-Bromo-2-ethylsulfanyl-6-methyl-chromen-4-one



[700] A mixture of 8-bromo-4-hydroxy-6-methyl-chromene-2-thione (20.0 g, 73.8 mmol), EtI (46 g, 295 mmol), and K₂CO₃ (12.2 g, 88.5 mmol) in acetone (200 mL) was stirred at 60°C for 3 h. When the reaction had cooled to rt, the mixture was diluted with water (200 mL) and extracted with DCM (2 x 200 mL). The combined organic extracts were concentrated and purified via silica gel chromatography eluted with 20%-40% EtOAc in petroleum ether to give the product as a gum. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.51 (t, J=7.2 Hz, 3 H), 2.45 (s, 3 H), 3.22 (q, J=7.2 Hz, 2 H), 6.32 (s, 1 H), 7.70 (s, 1 H), 7.93 (s, 1 H).

[701] Intermediate 14: 8-Acetyl-2-ethylsulfanyl-6-methyl-chromen-4-one



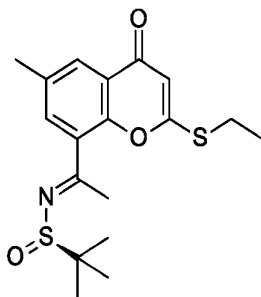
[702] A mixture of 8-bromo-2-ethylsulfanyl-6-methyl-chromen-4-one (9.00 g, 30.0 mmol), tributyl(1-ethoxyvinyl)tin (13.3 g, 36.8 mmol) and Pd(PPh₃)₂Cl₂ (2.11 g, 3.01 mmol) in dioxane (90 mL) was stirred at 95°C for 16 h. HCl (30 mL, 1 M) was added to the mixture and stirred at 50°C for 0.5 h. When cooled to rt, the mixture was treated with saturated aqueous KF (100 mL) and stirred for 0.5 h, then filtered. The filter cake was washed with EtOAc (3 x 40 mL). The filtrate was extracted with EtOAc (2 x 80 mL). The combined organic extracts were concentrated and purified on a silica

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gel column eluted with 0-60% EtOAc in petroleum ether to give the product as a solid (5.8 g, 60%).

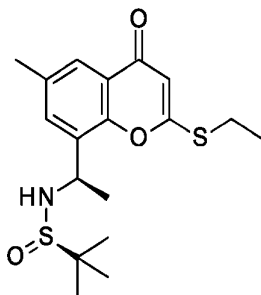
MS ES+ m/z 263 $[M+H]^+$.

[703] Intermediate 15: (NE,R)-N-[1-(2-Ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide



[704] A mixture of 8-acetyl-2-ethylsulfanyl-6-methyl-chromen-4-one (9.49 g, 36.2 mmol) and (R)-2-methylpropane-2-sulfinamide (8.77 g, 72.4 mmol) in THF (100 mL) was treated with $Ti(i-PrO)_4$ (41.1 g, 145 mmol) and stirred at 75°C for 16 h. The reaction was treated with additional (R)-2-methylpropane-2-sulfinamide (6.58 g, 54.3 mmol) and $Ti(i-PrO)_4$ (30.9 g, 109 mmol) and stirred at 75°C for another 16 h. The mixture was quenched with brine (200 mL), stirred for 0.5 h, and filtered. The filter cake was washed with EtOAc (300 mL). The aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated to give the product as a solid (13 g, crude). MS ES+ m/z 366 $[M+H]^+$.

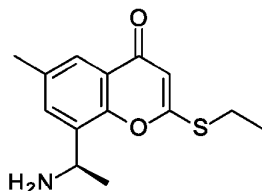
[705] Intermediate 16: (R)-N-[(1R)-1-(2-Ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide



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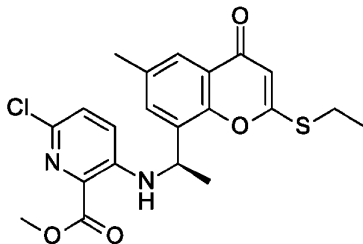
[706] A mixture of (NE,R)-N-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide (12.0 g, 32.8 mmol) in DCM (100 mL) and MeOH (100 mL) was treated with AcOH (15.8 g, 262 mmol) and NaBH₃CN (6.19 g, 98.5 mmol) at -10°C, and stirred at 25°C for 16 h. The mixture was quenched with NH₃·H₂O (250 mL) and extracted with DCM (3 x 200 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as a solid (11 g, isomer ratio: 3/2, crude). MS ES+ *m/z* 368 [M+H]⁺.

[707] Intermediate 17: 8-[(1R)-1-Aminoethyl]-2-ethylsulfanyl-6-methyl-chromen-4-one



[708] A mixture of (R)-N-[(1R)-1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide (6.00 g, 16.3 mmol) in EtOAc (40 mL) was treated with HCl (82 mL, 4 M in EtOAc) and stirred at 25°C for 16 h. The mixture was concentrated, diluted with water (100 mL), and washed with EtOAc (100 mL). The pH of the aqueous phase was adjusted to 8 with NH₃·H₂O (25%) and extracted with DCM (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as an oil (2.4 g, crude). MS ES+ *m/z* 264 [M+H]⁺.

[709] Intermediate 18: Methyl 6-chloro-3-[[[(1R)-1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate

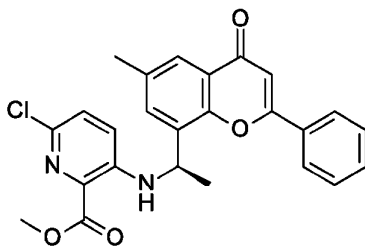


[710] A mixture of 8-[(1R)-1-aminoethyl]-2-ethylsulfanyl-6-methyl-chromen-4-one (880 mg, 3.34

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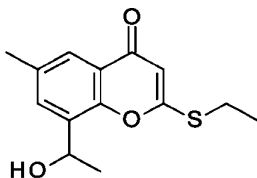
mmol), methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (950 mg, 5.01 mmol) and DIEA (2.16 g, 16.7 mmol) in DMF (10 mL) was stirred at 100°C for 21 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography eluted with 0%-35% EtOAc in petroleum ether to give the product as a solid (1.08 g, yield: 75%). MS ES+ *m/z* 433 [M+H]⁺.

[711] Intermediate 19: Methyl 6-chloro-3-[[[(1R)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate



[712] A mixture of methyl 6-chloro-3-[[[(1R)-1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate (150 mg, 346.48 μmol), phenylboronic acid (168.99 mg, 1.39 mmol), thiophene-2-carbonyloxycopper (132.14 mg, 692.97 μmol), Pd(PPh₃)₄ (40.04 mg, 34.65 μmol), and Cs₂CO₃ (338.67 mg, 1.04 mmol) in 2-MeTHF (2 mL) was stirred at 90°C for 24 h to give a black suspension. After cooling to rt, filtered the reaction and concentrated to a residue which was purified via flash silica gel chromatography using a gradient of EtOAc (0-30%) in petroleum ether to give the product as a yellow oil (88 mg, 54%). MS ES+ *m/z* 449 [M+H]⁺.

[713] Intermediate 20: 2-Ethylsulfanyl-8-(1-hydroxyethyl)-6-methyl-chromen-4-one

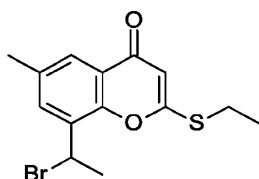


[714] A solution of 8-acetyl-2-ethylsulfanyl-6-methyl-chromen-4-one (8.30 g, 31.6 mmol) in DCM (30 mL) and MeOH (30 mL) was treated with NaBH₄ (1.32 g, 34.8 mmol) in portions at 0 °C, and

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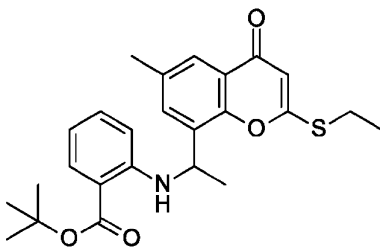
stirred at 15°C for 1 h. The mixture was diluted with water (50 mL) and extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified on a silica gel column eluted with 0-4% MeOH in DCM to give the product as a solid (6.0 g, 60%). MS ES+ *m/z* 265 [M+H]⁺.

[715] Intermediate 21: 8-(1-Bromoethyl)-2-ethylsulfanyl-6-methyl-chromen-4-one



[716] A mixture of 2-ethylsulfanyl-8-(1-hydroxyethyl)-6-methyl-chromen-4-one (5.50 g, 20.8 mmol) in DCM (50 mL) was treated dropwise with PBr₃ (16.9 g, 62.4 mmol) at 0°C, then stirred at 30°C for 4 h. The reaction was quenched with water (20 mL) at 0°C and the pH adjusted to 8 with saturated aqueous NaHCO₃. The mixture was extracted with DCM (2 x 80 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as an oil (4.7 g, 61%). MS ES+ *m/z* 329 [M+2+H]⁺.

[717] Intermediate 22: tert-Butyl 2-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate

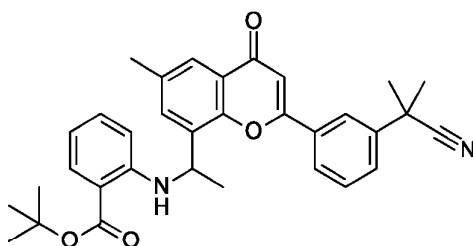


[718] 8-(1-Bromoethyl)-2-ethylsulfanyl-6-methyl-chromen-4-one (25.0 g, 76.4 mmol), tert-butyl 2-aminobenzoate (29.5 g, 153 mmol) and DIEA (14.8 g, 20.0 mL, 115 mmol) were combined with DMF (150 mL) in a 500 mL round bottom flask and heated at 80°C. After cooling to rt, the reaction was partially concentrated to ~100 mL, poured into 1.1 L of water, and extracted with EtOAc (2 x 350 mL). The combined organic layers were washed with brine (400 mL). The combined aqueous

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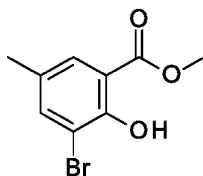
layers were re-extracted with fresh EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4 , filtered, and concentrated to give a thick oil. Purified the residue via silica gel chromatography using EtOAc in DCM (0% to 10%) to provide an off-white foam. Triturated with heptanes/DCM and washed with heptanes to give the product as a white solid (27.1 g, 81%). MS ES^+ m/z 440 $[\text{M}+\text{H}]^+$.

[719] Intermediate 23: tert-Butyl 2-[1-[2-[3-(1-cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoate



[720] Combined tert-butyl 2-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate (150 mg, 341 μmol), (3-(2-cyanopropan-2-yl)phenyl)boronic acid (96.8 mg, 512 μmol), tris(dibenzylideneacetone)dipalladium(0) (31.2 mg, 34.1 μmol), copper(I) thiophene-2-carboxylate (97.6 mg, 512 μmol), cesium carbonate (334 mg, 1.02 mmol), and tri(2-furyl)phosphine (7.92 mg, 34.1 μmol) in 1,4-dioxane (5 mL) and heated at 85°C for 12 h. The crude product mixture was filtered, concentrated, and purified using silica column (10-80% ethyl acetate in heptane) to afford the product (110.0 mg, 62%). MS ESI^+ m/z 523 $[\text{M}+\text{H}]^+$.

[721] Intermediate 24: Methyl 3-bromo-2-hydroxy-5-methyl-benzoate

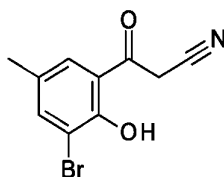


[722] Bromine (1.0 g, 6.3 mmol) was added to a stirred mixture of methyl 2-hydroxy-5-methylbenzoate (1.0 g, 0.87 mL, 6.0 mmol) and sodium acetate (0.74 g, 9.0 mmol) in AcOH (5 mL) at rt. After 15 min, added water (20 mL) and filtered. The solids were washed with water (5 mL) and

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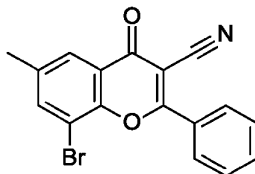
assumed quantitative yield. MS ES+ m/z 245,247 $[M+H]^+$.

[723] Intermediate 25: 3-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-oxo-propanenitrile



[724] Sodium hydride (408 mg, 60% wt, 10.2 mmol) was added to a solution of methyl 3-bromo-2-hydroxy-5-methylbenzoate (1.00 g, 4.08 mmol) in THF (5 mL) at rt. After ~65 minutes, acetonitrile (234 μ L, 4.49 mmol) was added to the above mixture and the reaction allowed to stir at rt for ~2 h. Concentrated the reaction and added EtOAc and AcOH to the residue and diluted with heptanes. The resulting solids were removed by filtration and washed with heptanes to give the product as an orange solid (0.95 g, 92%). MS ES+ m/z 254,256 $[M+H]^+$.

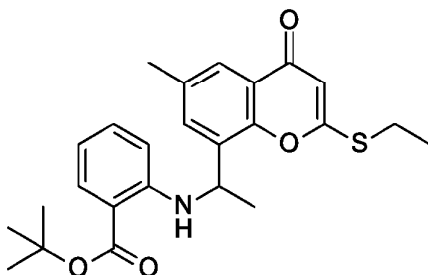
[725] Intermediate 26: 8-Bromo-6-methyl-4-oxo-2-phenyl-chromene-3-carbonitrile



[726] Benzoyl chloride (74.1 mg, 61.3 μ L, 527 μ mol) was added to 3-(3-bromo-2-hydroxy-5-methylphenyl)-3-oxopropanenitrile (134 mg, 527 μ mol) in pyridine (4 mL) at rt. After 90 min, toluene (2 mL) was added and the reaction mixture was concentrated. The crude product was purified by column chromatography, eluting with DCM, to give the product (115 mg, 64%). MS ES+ m/z 340,342 $[M+H]^+$.

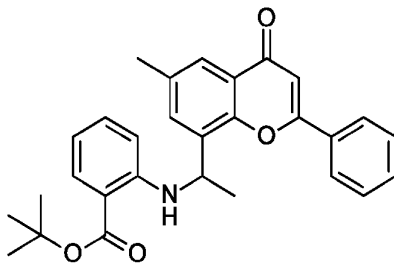
[727] Intermediate 27 and Intermediate 28: tert-Butyl 2-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate, Isomer 1 and Isomer 2

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[728] tert-Butyl 2-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate (22.04 g, 50.14 mmol) was separated into component isomers using a Chiralcel OJ column (8 x 34 cm; 20 micron) eluted with 100% MeOH with 0.2% DMEA to give isomer 1 (wet 11.3 g) and isomer 2 (wet 12.9 g). MS ES+ m/z 440 $[M+H]^+$.

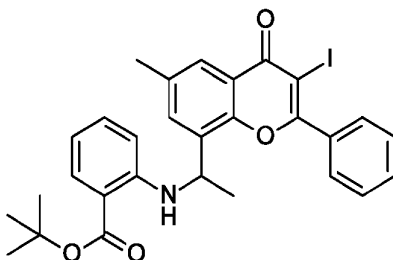
[729] Intermediate 29: tert-Butyl 2-[1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2



[730] Combined tert-butyl 2-[1-(2-ethylsulfanyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate, Isomer 2 (1.00 g, 2.27 mmol), phenylboronic acid (0.56 g, 4.55 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.21 g, 0.23 mmol), copper(I) thiophene-2-carboxylate (0.87 g, 4.55 mmol), zinc(II) acetate (0.84 g, 4.55 mmol), and tri(2-furyl)phosphine (0.26 g, 1.14 mmol) in 1,4-dioxane (20 mL) and heated at 85°C for 12 h. The crude product mixture was purified using silica column (10-60% ethyl acetate in heptane), then reversed phase chromatography (0-100% acetonitrile in water, with 0.1% TFA) to afford the product (0.53 g, 48%). MS ES+ m/z 456 $[M+H]^+$.

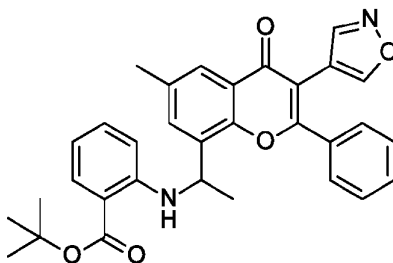
[731] Intermediate 30: tert-Butyl 2-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2

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[732] A dry flask equipped with a stir bar and septum was flushed with argon gas and then charged with tert-butyl 2-[1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2 (0.53 g, 1.16 mmol) and 3 mL of dry THF. The reaction was cooled in an ice bath. When cold, 2,2,6,6-tetramethylpiperidinylzinc chloride lithium chloride complex (1M in THF, 3.5 mL, 3.50 mmol) was added dropwise via addition funnel over 30 min. After addition was complete, allowed the reaction to stir at rt for 7 h. The reaction was cooled in an ice bath and iodine in dry THF (1M, 1.39 mL, 1.39 mmol) was added dropwise via addition funnel. After addition was complete, the reaction was stirred at 0°C for 1 h and rt for 12 h. The reaction was cooled to -40°C and quenched with methanol (10 mL). Added 50 mL of an ammonium chloride/ammonia solution (aqueous 2M solution; 50 mL) and stirred the reaction at rt for 2 h. Extracted three times with 300 mL of dichloromethane. The organics were combined, washed with aqueous sodium carbonate, collected, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by reversed phase chromatography (0-100% acetonitrile in water, with 0.1% TFA), then using silica column (0-40% ethyl acetate in heptane) to give the product (0.43 g, 61%). MS ES+ *m/z* 582 [M+H]⁺.

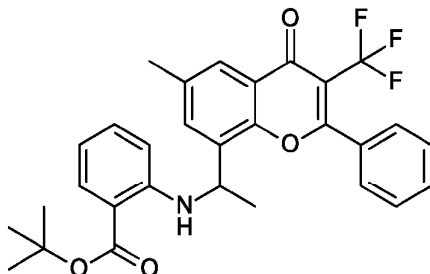
[733] Intermediate 31: tert-Butyl 2-[1-(3-isoxazol-4-yl-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2



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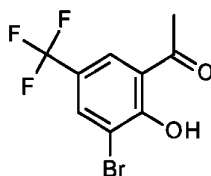
[734] Combined tert-butyl 2-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2 (0.34 g, 0.58 mmol), 1,2-oxazol-4-ylboronic acid (0.098 g, 0.87 mmol), potassium phosphate (0.25 g, 1.16 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride (0.043 g, 0.058 mmol) in THF:water (4:1, 20 mL) and heated at 80°C for 16 h. The crude product mixture was purified using silica column (0-10% ethyl acetate in DCM) to afford the product (0.052 g, 16%). MS ES+ m/z 523 [M+H]⁺.

[735] Intermediate 32: tert-Butyl 2-[1-[6-methyl-4-oxo-2-phenyl-3-(trifluoromethyl)chromen-8-yl]ethylamino]benzoate, Isomer 2



[736] Combined tert-butyl 2-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate, Isomer 2 (0.086 g, 0.15 mmol), copper(I) iodide (0.034 g, 0.18 mmol), and methyl difluoro(fluorosulfonyl)acetate (0.14 g, 0.74 mmol) in DMF (2 mL) and stirred for 18 h. The reaction mixture was cooled to rt and quenched with saturated aqueous ammonium chloride (1 mL). Extracted two times with 1 mL of dichloromethane. The organics were combined, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica column (0-20% ethyl acetate in DCM) to give the product (0.053 g, 68%). MS ES+ m/z 524 [M+H]⁺.

[737] Intermediate 33: 1-[3-Bromo-2-hydroxy-5-(trifluoromethyl)phenyl]ethanone



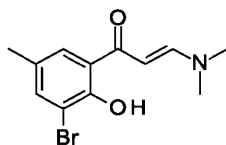
[738] To a mixture of 2-bromo-4-(trifluoromethyl)phenol (50.0 g, 207 mmol) in 1,4-dioxane (400

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mL) was added Pd(PPh₃)₂Cl₂ (7.28 g, 10.37 mmol) and tributyl(1-ethoxyvinyl)stannane (90.0 g, 249 mmol) under N₂ atmosphere, and stirred at 95 °C for 16 h. To the reaction was added HCl (1 M, 207 mL) and stirred at 50 °C for 1 h. When cooled to rt, to the mixture was added saturated aqueous potassium fluoride (200 mL), stirred for 0.5 h and filtered. The aqueous layer was extracted with DCM (100 mL x2). The combined organic layer was washed with brine (150 mL x2), dried over anhydrous Na₂SO₄, filtered and concentrated to give 1-[2-hydroxy-5-(trifluoromethyl)phenyl]ethanone (31 g, crude).

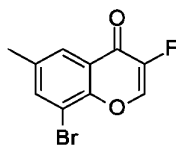
[739] A mixture of bromine (29.0 g, 182 mmol) in AcOH (50 mL) was added to a mixture of 1-[2-hydroxy-5-(trifluoromethyl)phenyl]ethanone (31.0 g, 152 mmol) and sodium acetate (15.0 g, 182 mmol) in AcOH (250 mL) dropwise at 0 °C, and stirred at 20 °C for 16 h. The reaction mixture was poured into ice and water (500 mL) and filtered. The filter cake was dried in vacuum to give the product (31 g, yield: 72%).

[740] Intermediate 34: (E)-1-(3-Bromo-2-hydroxy-5-methyl-phenyl)-3-(dimethylamino)prop-2-en-1-one



[741] Combined 1-(3-bromo-2-hydroxy-5-methyl-phenyl)ethenone (13.06 g, 57.01 mmol) and N,N-dimethylformamide dimethyl acetal (7.57 mL, 57.01 mmol) in toluene (45 mL) and stirred at 80°C for 1 h. The reaction mixture was concentrated to dryness, taken up in hot ethyl acetate/heptane, and filtered to remove solids that were discarded. The filtrate was concentrated until material crystallized, then filtered. The solids were washed with heptane and dried to give product (9.92 g, 61%) that was used in the next reaction.

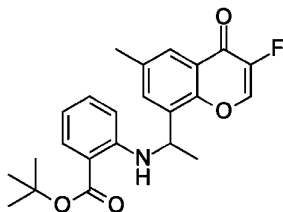
[742] Intermediate 35: 8-Bromo-3-fluoro-6-methyl-chromen-4-one



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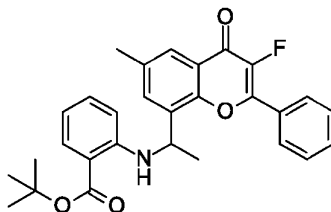
[743] To a stirred solution of (E)-1-(3-bromo-2-hydroxy-5-methyl-phenyl)-3-(dimethylamino)prop-2-en-1-one (9.92 g, 34.91 mmol) in THF (140 mL) was added N-chloromethyl-N-fluorotriethylenediammonium bis(tetrafluoroborate) (12.37 g, 34.91 mmol). After 4 h, the reaction mixture was concentrated to dryness. The residue was purified by silica column (0-10% ethyl acetate in heptane) to give the product (4.14 g, 44%). MS ES+ m/z 257 [M+H]⁺.

[744] Intermediate 36: tert-Butyl 2-[1-(3-fluoro-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate



[745] Intermediate 36 can be made according to the foregoing Intermediates. MS ES+ m/z 398 [M+H]⁺.

[746] Intermediate 37: tert-Butyl 2-[1-(3-fluoro-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoate



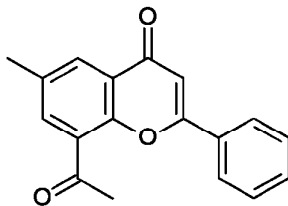
[747] A dry flask equipped with a stir bar and septum was flushed with argon gas and then charged with tert-butyl 2-[1-(3-fluoro-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate (0.23 g, 0.57 mmol) and magnesium chloride (0.4 M in dry THF, 5.24 mL, 2.09 mmol). The reaction was cooled to -5°C. When cold, 2,2,6,6-tetramethylpiperidinyllzinc chloride lithium chloride complex (1M in THF, 2.26 mL, 2.26 mmol) was added dropwise via addition funnel. After addition was complete, allowed the reaction to stir at 0°C for 30 min. Added iodine (1M in dry THF, 1.13 mL, 1.13 mmol) dropwise via addition funnel over 30 min. Diluted with dichloromethane and washed with aqueous sodium thiosulfate. The organics were dried over Na₂SO₄, filtered, and concentrated. The residue

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was purified by silica column (0-100% ethyl acetate in heptane) to give tert-butyl 2-[1-(3-fluoro-2-iodo-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate (0.14 g, 45%). MS ES+ m/z 524 [M+H]⁺.

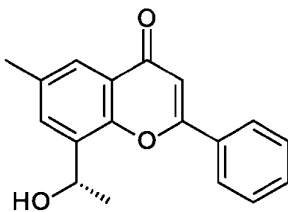
[748] Combined tert-butyl 2-[1-(3-fluoro-2-iodo-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoate (0.13 g, 0.25 mmol), phenylboronic acid (0.045 g, 0.37 mmol), potassium phosphate (0.11 g, 0.50 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride (0.018 g, 0.025 mmol) in THF:water (4:1, 20 mL) and heated at 80°C for 15 min. The crude product mixture was concentrated, then purified using silica column (0-30% ethyl acetate in heptane) to afford the product (0.060 g, 51%). MS ES+ m/z 474 [M+H]⁺.

[749] Intermediate 38: 8-Acetyl-6-methyl-2-phenyl-chromen-4-one



[750] Intermediate 38 can be made according to the foregoing Intermediates. MS ES+ m/z 279 [M+H]⁺.

[751] Intermediate 39: 8-[(1S)-1-Hydroxyethyl]-6-methyl-2-phenyl-chromen-4-one

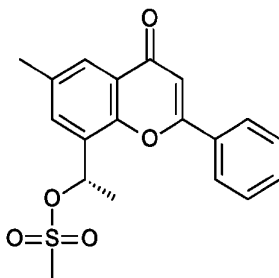


[752] A solution of 8-acetyl-6-methyl-2-phenyl-chromen-4-one (30 g, 108 mmol), formic acid (14.9 g, 324 mmol), and RuCl(p-cymene)[(S,S)-Ts-DPEN] (CAS 192139-90-5, 2.04 g, 3.24 mmol) in DCM (300 mL) was stirred at 0-5°C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (4.93 g, 324 mmol) was added dropwise, maintaining the temperature below 10°C. The reaction was stirred at room temperature for 14 h. Diluted with DCM (300 mL) and washed with saturated aqueous sodium bicarbonate and brine. The organics were concentrated, slurried in acetonitrile (150 mL) for 30 min,

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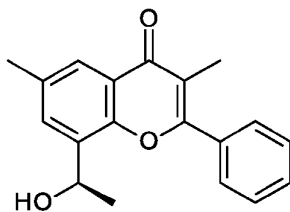
and filtered to afford the product (27.8 g, 91%). MS ES+ m/z 281 $[M+H]^+$.

[753] Intermediate 40: [(1S)-1-(6-Methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl] methanesulfonate



[754] A solution of 8-[(1S)-1-hydroxyethyl]-6-methyl-2-phenyl-chromen-4-one (30 g, 107 mmol) in DCM (300 mL) was stirred at 0-5°C. Methanesulfonic anhydride (54.7 g, 314 mmol) was added, followed by dropwise addition of diisopropylethylamine (41.5 g, 321 mmol), maintaining the temperature below 15°C. The reaction was stirred at room temperature for 2 h. Diluted with DCM (150 mL) and washed with saturated aqueous sodium bicarbonate and brine. The organics were dried over magnesium sulfate, filtered, and concentrated to afford the product (48.6 g, 100%). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.84 (d, $J=6.5\text{Hz}$, 3H), 2.40 (s, 6H), 6.33 (q, $J=6.3\text{ Hz}$, 1H), 7.10 (s, 1H), 7.59-7.67 (m, 3H), 7.81 (d, $J=2.3\text{Hz}$, 1H), 7.90-7.94 (m, 1H), 8.12-8.20 (m, 2H).

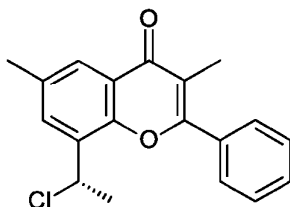
[755] Intermediate 41: 8-[(1R)-1-Hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one



[756] Intermediate 41 can be made according to the foregoing Intermediates. MS ES+ m/z 295 $[M+H]^+$.

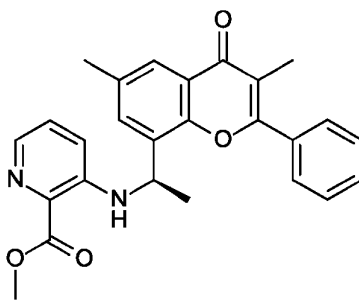
[757] Intermediate 42: 8-[(1S)-1-Chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one

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[758] A solution of 8-[(1R)-1-hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (20 g, 68.0 mmol) in cyclopentyl methyl ether (200 mL) was stirred at room temperature. 2,4,6-Trichloro[1,3,5]triazine (12.5 g, 68.0 mmol) was added, followed by DMF (7.9 mL, 102 mmol). The reaction was stirred at room temperature for 14 h. Diluted with 2M aqueous sodium hydroxide (100 mL) and separated the layers. The organics were washed with water (100 mL)/saturated aqueous sodium bicarbonate (100 mL) and 5% aqueous lithium chloride (100 mL). The organics were concentrated and diluted with isopropanol (120 mL). The slurry was heated at 45°C for 2 h and cooled to room temperature. Water (80 mL) was slowly added. Filtered to afford the product (18.4 g, 87%, 94% ee). MS ES+ m/z 313 [M+H]⁺.

[759] Intermediate 43: Methyl 3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate

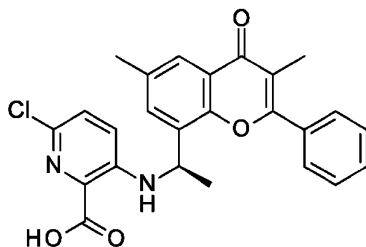


[760] A solution of 8-[(1S)-1-chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (5.0 g, 16 mmol) and methyl 3-aminopicolinate (15 g, 96 mmol) in *tert*-amyl alcohol (25 mL) was stirred at room temperature. Triethylamine (8.9 mL, 64 mmol) was added. The reaction was stirred at 100°C for 24 h, cooled to room temperature, and concentrated. Diluted with methyl *tert*-butyl ether (25 mL) and 1M aqueous hydrochloric acid (25 mL). Filtered to afford the product (4.7 g, 68%). MS ES+ m/z 429

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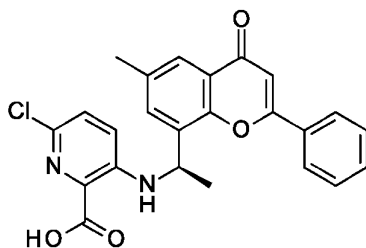
 $[M+H]^+$.

[761] Example 1: 6-Chloro-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid



[762] A mixture of methyl 6-chloro-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate (1 g, 2.16 mmol) and NaOH (2 M, 7.35 mL) in MeOH (20 mL) was stirred at 45°C for 2 h to give a white suspension. Added 10 mL of water, adjusted the pH to 3 with 2M aqueous HCl, and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was triturated with acetonitrile (5 mL) to give the product as a white solid (418 mg, 42%). MS ES+ *m/z* 449 $[M+H]^+$.

[763] Example 2: 6-Chloro-3-[[[(1R)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid

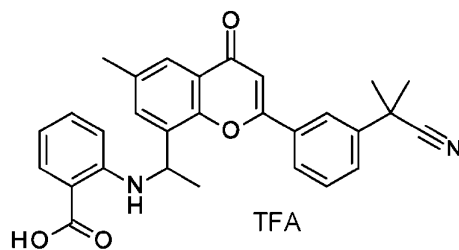


[764] Solid NaOH (124.74 mg, 3.12 mmol) was dissolved in water (0.7 mL) and added to the mixture of methyl 6-chloro-3-[[[(1R)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylate (700.00 mg, 1.56 mmol) in MeOH (7 mL). The mixture was stirred at 50°C for 1 hour to give a yellow suspension. The reaction was poured into water (100 mL),

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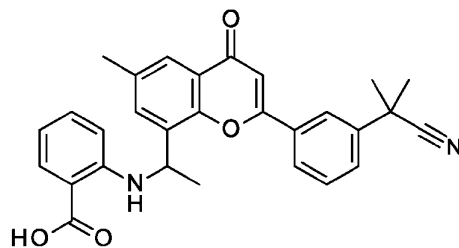
the pH adjusted to 2 with aqueous HCl (2 M), and the mixture extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to a residue. The residue was triturated with refluxing acetonitrile (2 x 5 mL) to give the product as a light yellow solid (293 mg, 43%). MS ES+ m/z 435 [M+H]⁺.

[765] Example 3: 2-[1-[2-[3-(1-Cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid



[766] Combined tert-butyl 2-[1-[2-[3-(1-cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoate (110.0 mg, 210.5 μ mol) and TFA (3.0 g, 2.0 mL, 26 mmol) in DCM (2 mL) and heated at 40°C for 3 hours. Concentrated the reaction and purified using a C-18 column, eluted with 10-90% acetonitrile in water (0.1% TFA additive), to give the product (45.0 mg, 46%). MS ES+ m/z 467 [M+H]⁺.

[767] Example 4 and Example 5: 2-[1-[2-[3-(1-Cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1 and Isomer 2

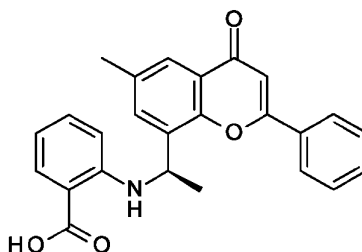


[768] Dissolved 2-[1-[2-[3-(1-cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid (40 mg) in MeOH (2.25 mL) and DCM (2.25 mL). Separated via supercritical fluid chromatography (Chiralpak AS-H, 250 mm x 21 mm; 20%

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MeOH w/ 0.5% DMEA : 80% CO₂) to obtain the product isomers (20 mg, 19 mg). MS ES+ m/z 467 [M+H]⁺, for both.

[769] Example 22: 2-[[[(1R)-1-(6-Methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid

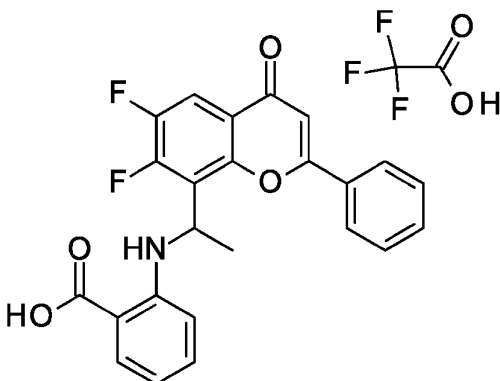
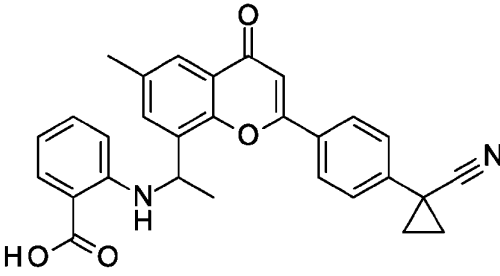
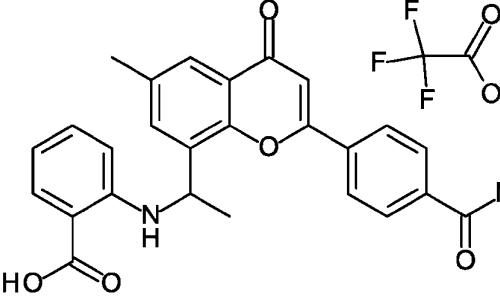


[770] A solution of [[(1S)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl] methanesulfonate (48.6 g, 107 mmol) in DCM (480 mL) was stirred at room temperature. Anthranilic acid (44.0 g, 321 mmol), followed slowly by 2,6-lutidine (22.9 g, 214 mmol) was added. The reaction was stirred at room temperature for 14 h. Diluted with DCM (240 mL) and washed with 1M aqueous hydrochloric acid (3 x 240 mL) and brine. The organics were dried over magnesium sulfate, filtered, and concentrated. Slurried in acetonitrile (200 mL) for 30 min and filtered to afford the product as a yellow solid (24.2 g, 57%). MS ES- m/z 398 [M-H]⁻.

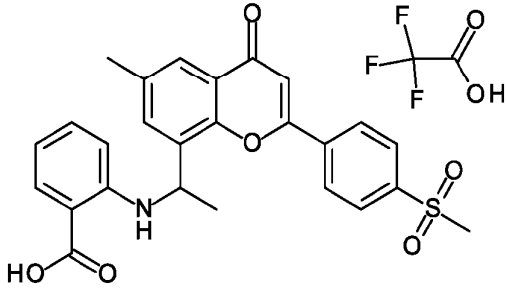
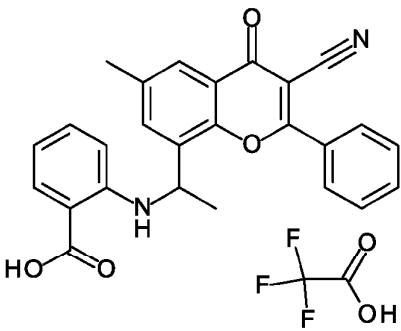
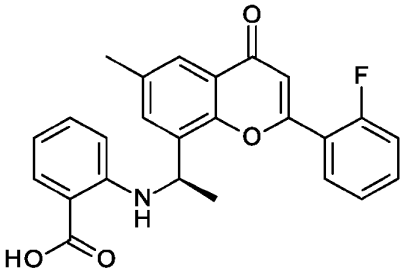
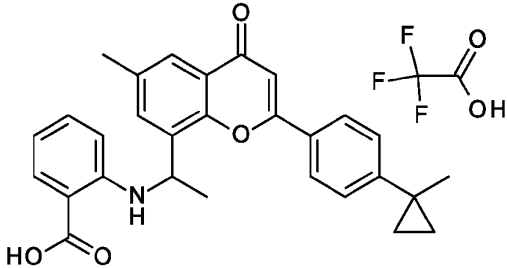
[771] The following compounds in Table 1 can be made according to Schemes 1-4 or the foregoing Examples.

Table 1

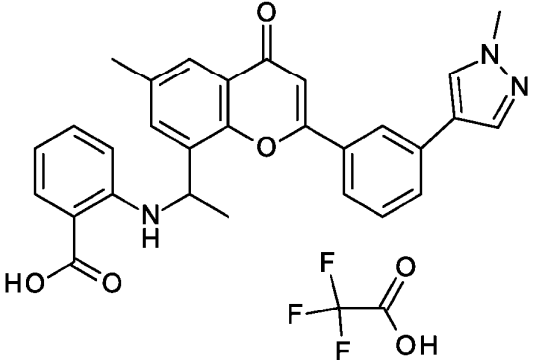
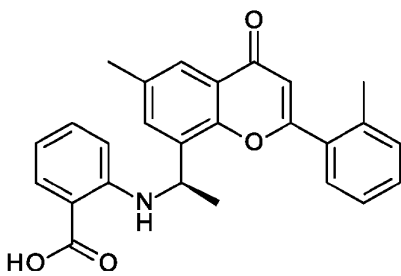
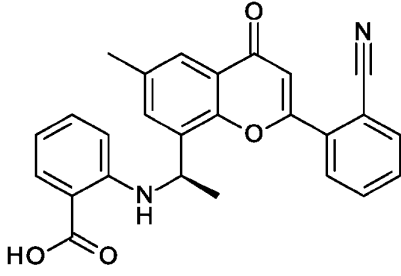
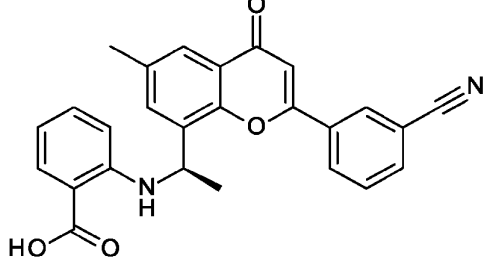
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Example #	Chemical Name	Structure	MS ES+ m/z
6	2-[1-(6,7-Difluoro-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		422 [M+H] ⁺
7	2-[1-[2-[4-(1-Cyanocyclopropyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid		465 [M+H] ⁺
8	2-[1-[2-[4-(Dimethylcarbamoyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		471 [M+H] ⁺

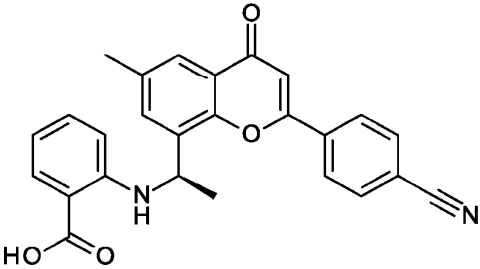
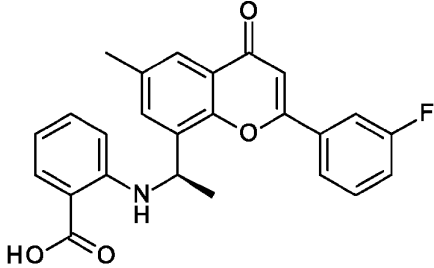
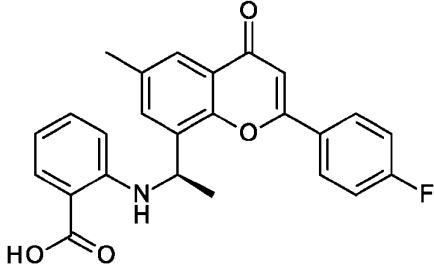
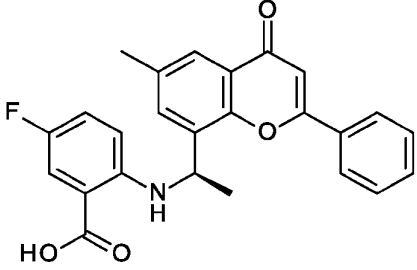
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9	2-[1-[6-Methyl-2-(4-methylsulfonylphenyl)-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		478 [M+H] ⁺
10	2-[1-(3-Cyano-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		425 [M+H] ⁺
11	2-[[1-(1R)-1-[2-(2-Fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		418 [M+H] ⁺
12	2-[1-[6-Methyl-2-[4-(1-methylcyclopropyl)phenyl]-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		454 [M+H] ⁺

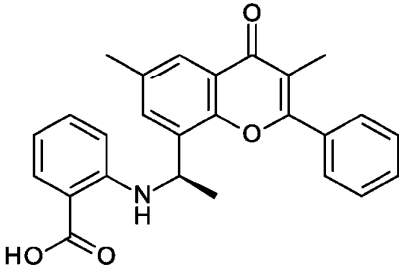
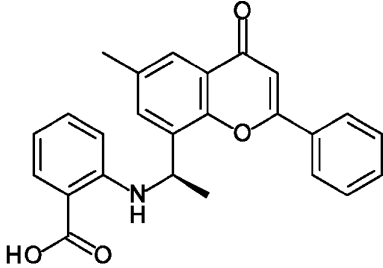
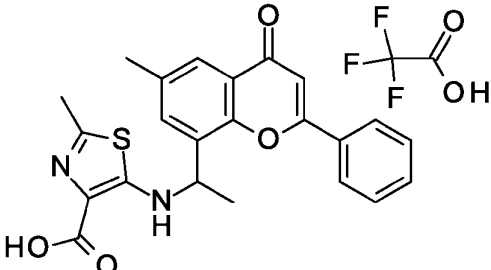
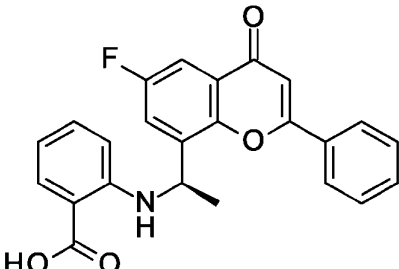
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13	2-[1-[6-Methyl-2-[3-(1-methylpyrazol-4-yl)phenyl]-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		480 [M+H] ⁺
14	2-[[[(1R)-1-[6-Methyl-2-(o-tolyl)-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		414 [M+H] ⁺
15	2-[[[(1R)-1-[2-(2-Cyanophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		425 447 [M+Na] ⁺
16	2-[[[(1R)-1-[2-(3-Cyanophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		425 [M+H] ⁺

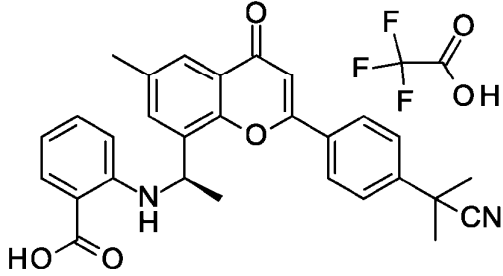
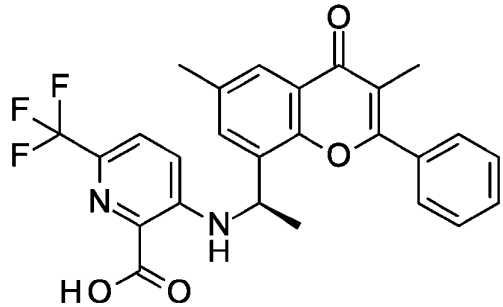
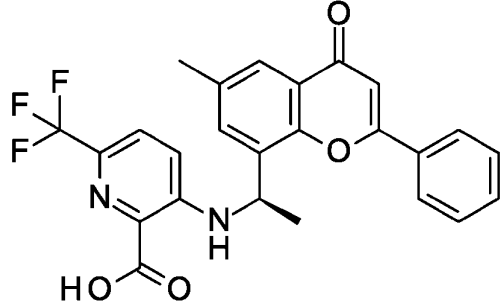
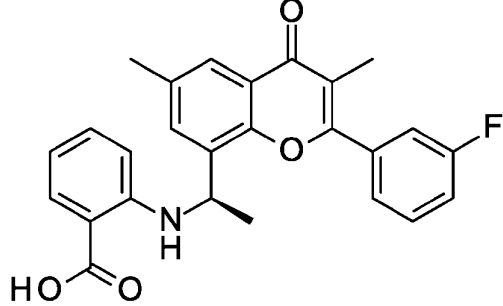
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17	2-[[[(1R)-1-[2-(4-Cyanophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		425 [M+H] ⁺
18	2-[[[(1R)-1-[2-(3-Fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		418 [M+H] ⁺
19	2-[[[(1R)-1-[2-(4-Fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		418 [M+H] ⁺
20	5-Fluoro-2-[[[(1R)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		418 [M+H] ⁺

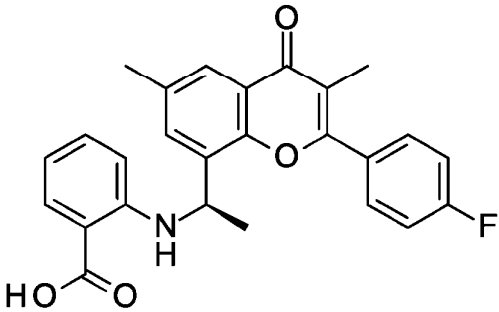
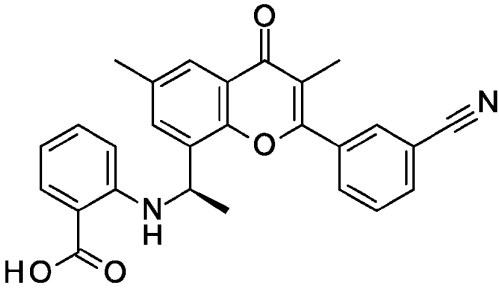
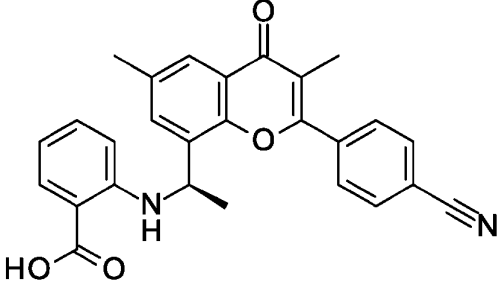
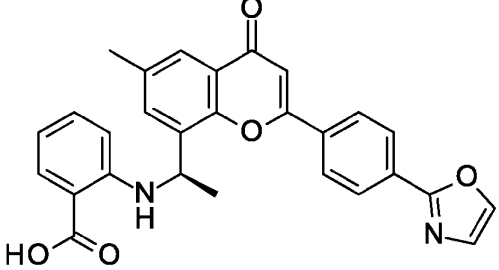
- 333 -

21	2-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		414 [M+H] ⁺
22	2-[[[(1R)-1-(6-Methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		400 [M+H] ⁺
23	2-Methyl-5-[1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]thiazole-4-carboxylic acid 2,2,2-trifluoroacetic acid		421 [M+H] ⁺
24	2-[[[(1R)-1-(6-Fluoro-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		404 [M+H] ⁺

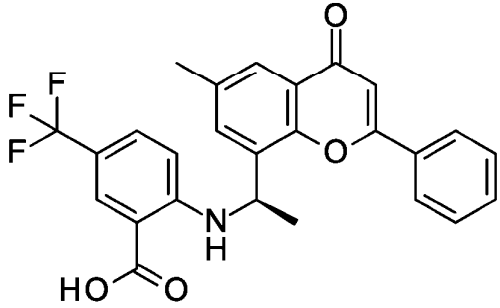
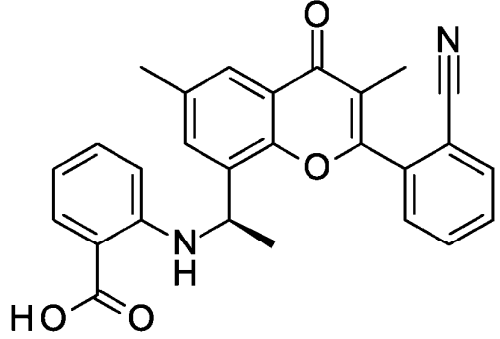
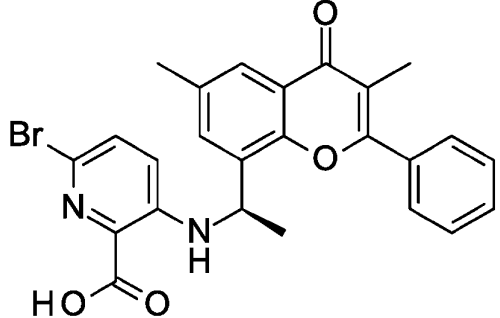
- 334 -

25	2-[[[(1R)-1-[2-[4-(1-Cyano-1-methyl-ethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		467 [M+H] ⁺
26	3-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-6-(trifluoromethyl)pyridine-2-carboxylic acid		483 [M+H] ⁺
27	3-[[[(1R)-1-(6-Methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-6-(trifluoromethyl)pyridine-2-carboxylic acid		469 [M+H] ⁺
28	2-[[[(1R)-1-[2-(3-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		432 [M+H] ⁺

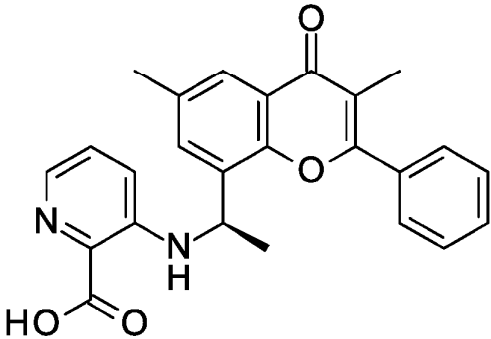
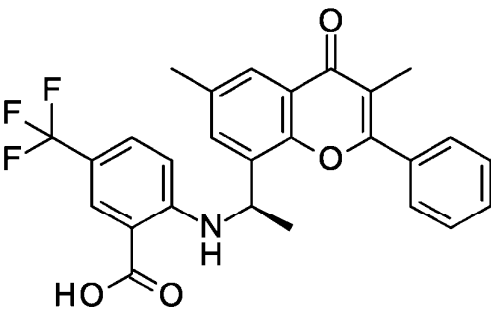
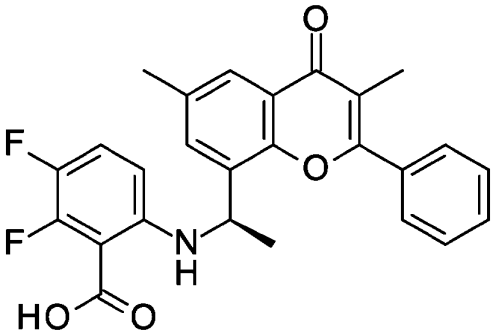
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29	2-[[[(1R)-1-[2-(4-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		432 [M+H] ⁺
30	2-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		439 [M+H] ⁺
31	2-[[[(1R)-1-[2-(4-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		439 [M+H] ⁺
32	2-[[[(1R)-1-[6-Methyl-2-(4-oxazol-2-ylphenyl)-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		467 [M+H] ⁺

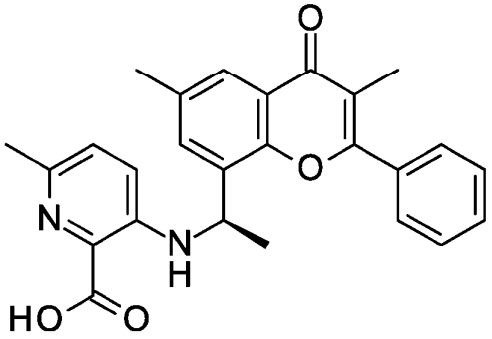
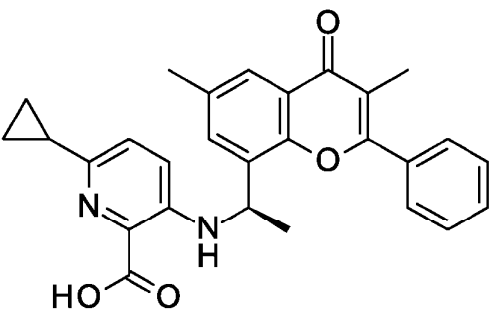
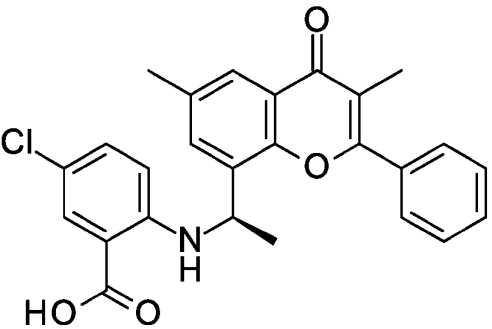
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33	2-[[[(1R)-1-(6-Methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-5-(trifluoromethyl)benzoic acid		468 [M+H] ⁺
34	2-[[[(1R)-1-[2-(2-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		439 [M+H] ⁺
35	6-Bromo-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid		494 [M+H] ⁺

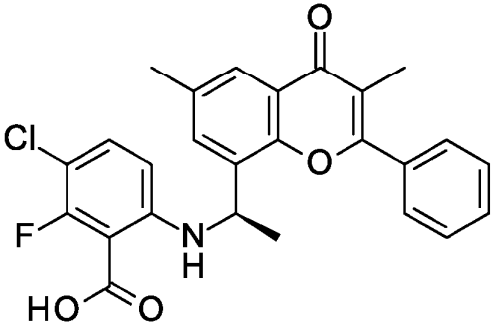
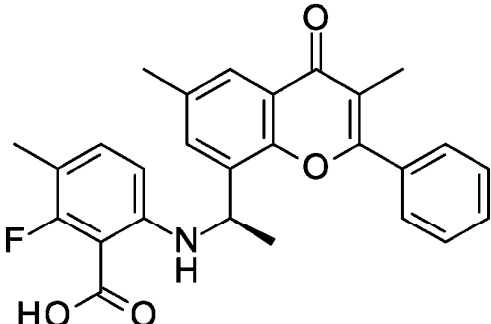
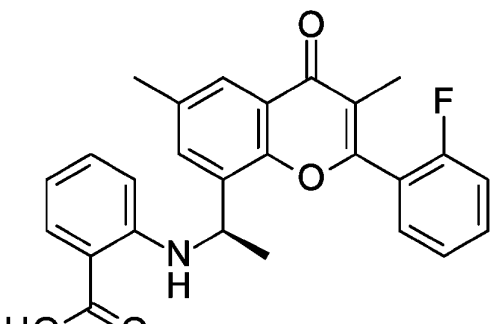
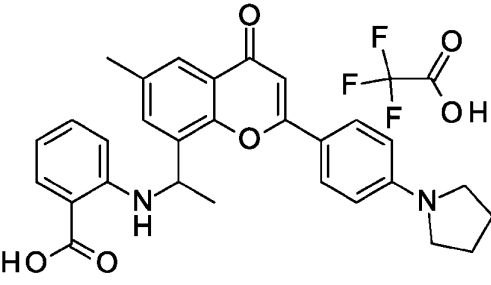
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36	3-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid		415 [M+H] ⁺
37	2-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-5-(trifluoromethyl)benzoic acid		482 [M+H] ⁺
38	6-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-2,3-difluoro-benzoic acid		450 [M+H] ⁺

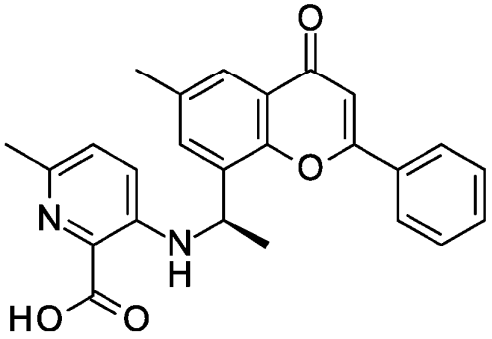
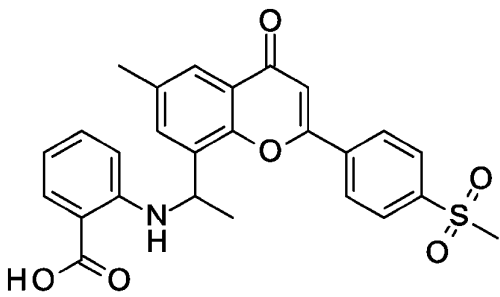
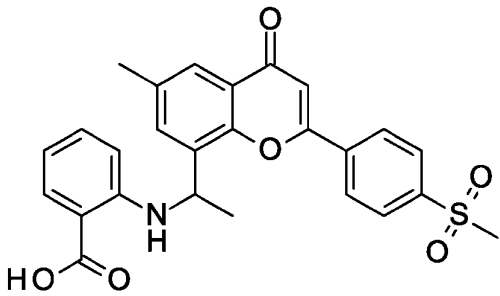
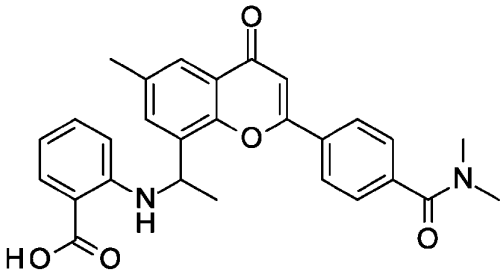
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39	3-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-6-methyl-pyridine-2-carboxylic acid		429 [M+H] ⁺
40	6-Cyclopropyl-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid		455 [M+H] ⁺
41	5-Chloro-2-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		448 [M+H] ⁺

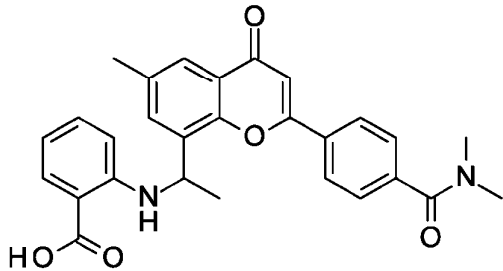
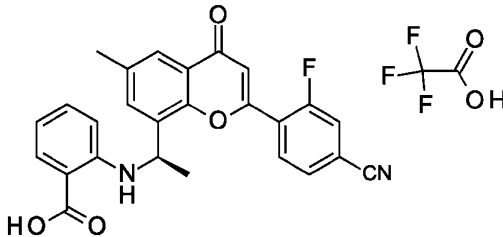
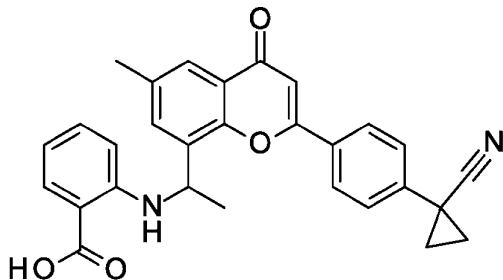
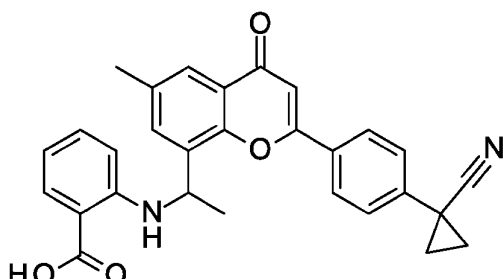
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42	3-Chloro-6-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-2-fluoro-benzoic acid		466 [M+H] ⁺
43	6-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-2-fluoro-3-methyl-benzoic acid		446 [M+H] ⁺
44	2-[[[(1R)-1-[2-(2-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		432 [M+H] ⁺
45	2-[1-[6-Methyl-4-oxo-2-(4-pyrrolidin-1-ylphenyl)chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		469 [M+H] ⁺

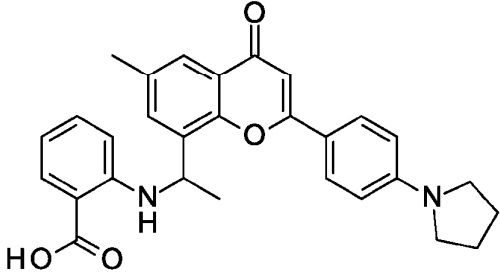
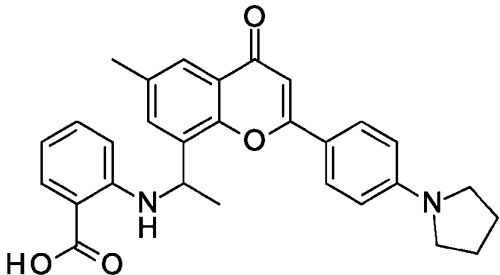
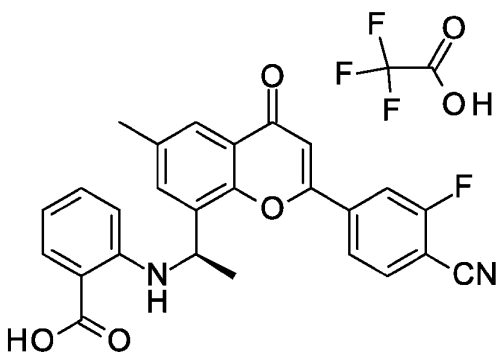
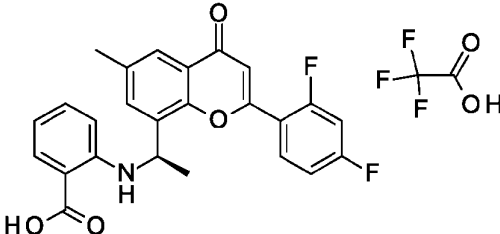
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46	6-Methyl-3-[[[(1R)-1-(6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid		415 [M+H] ⁺
47	2-[1-[6-Methyl-2-(4-methylsulfonylphenyl)-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		478 [M+H] ⁺
48	2-[1-[6-Methyl-2-(4-methylsulfonylphenyl)-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		478 [M+H] ⁺
49	2-[1-[2-[4-(Dimethylcarbamoyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		471 [M+H] ⁺

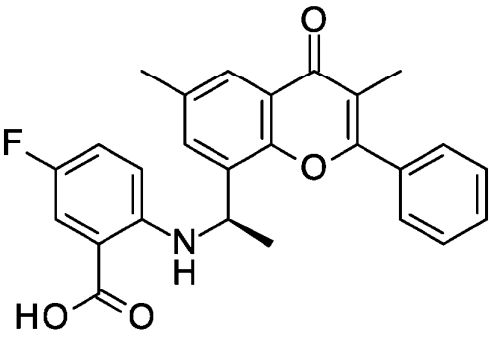
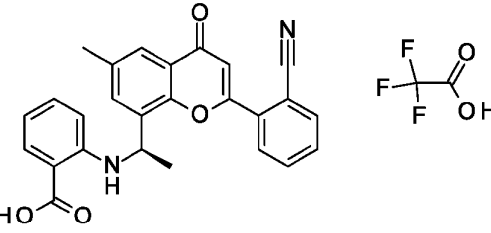
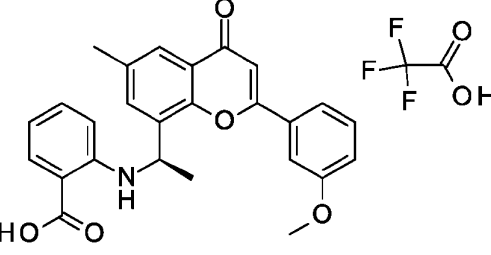
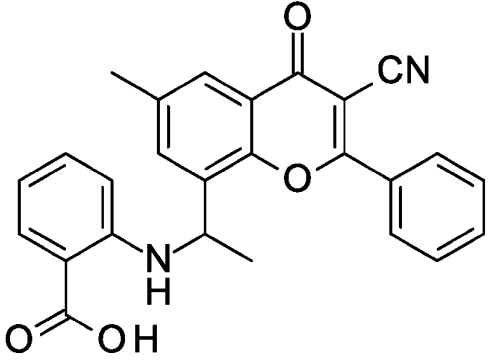
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50	2-[1-[2-[4-(Dimethylcarbamoyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		471 [M+H] ⁺
51	2-[[[(1R)-1-[2-(4-Cyano-2-fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		443 [M+H] ⁺
52	2-[1-[2-[4-(1-Cyanocyclopropyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		465 [M+H] ⁺
53	2-[1-[2-[4-(1-Cyanocyclopropyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		465 [M+H] ⁺

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54	2-[1-[6-Methyl-4-oxo-2-(4-pyrrolidin-1-ylphenyl)chromen-8-yl]ethylamino]benzoic acid, Isomer 1		469 [M+H] ⁺
55	2-[1-[6-Methyl-4-oxo-2-(4-pyrrolidin-1-ylphenyl)chromen-8-yl]ethylamino]benzoic acid, Isomer 2		469 [M+H] ⁺
56	2-[[1-(1R)-1-[2-(4-Cyano-3-fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		443 [M+H] ⁺
57	2-[[1-(1R)-1-[2-(2,4-Difluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		436 [M+H] ⁺

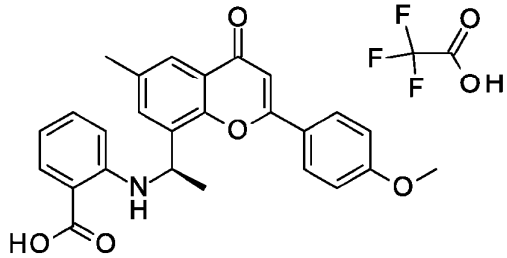
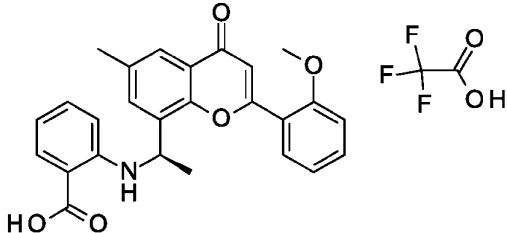
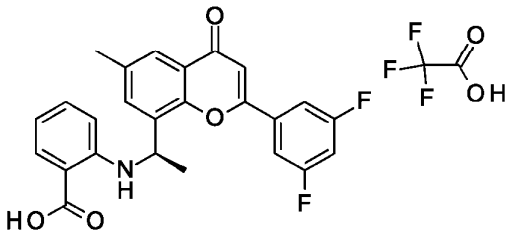
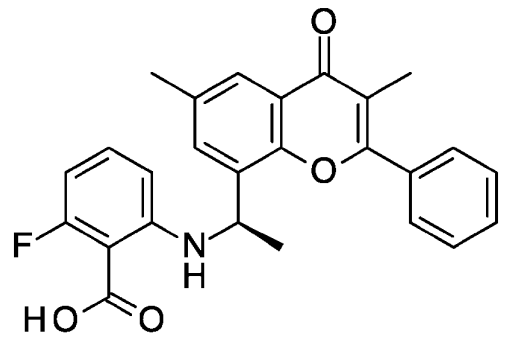
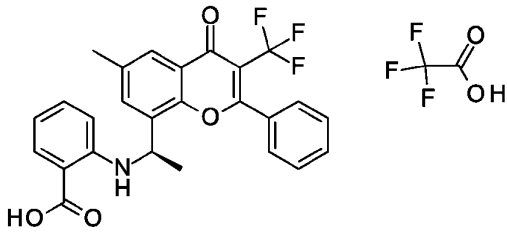
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58	2-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-5-fluoro-benzoic acid		432 [M+H] ⁺
59	2-[[[(1R)-1-[2-(2-Cyanophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		425 [M+H] ⁺
60	2-[[[(1R)-1-[2-(3-Methoxyphenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		430 [M+H] ⁺
61	2-[1-(3-Cyano-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid, Isomer 1		425 [M+H] ⁺

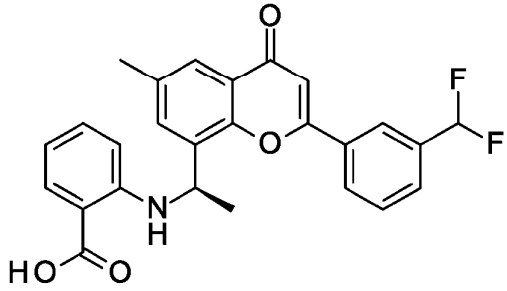
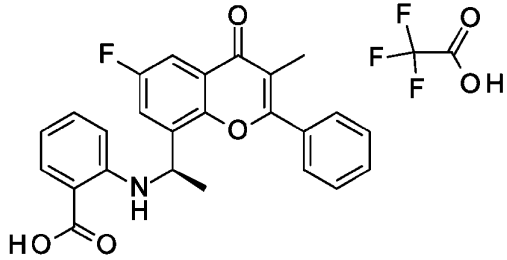
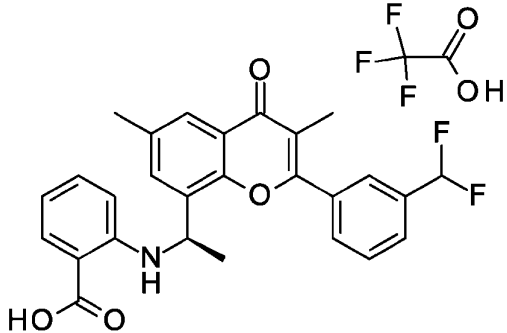
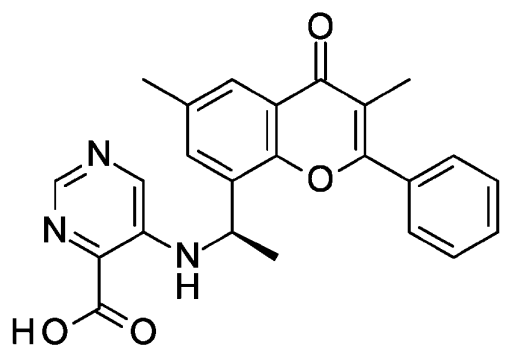
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62	2-[1-(3-Cyano-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid, Isomer 2		425 [M+H] ⁺
63	2-[[[(1R)-1-[2-(3,4-Difluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		436 [M+H] ⁺
64	2-[1-(5,6-Difluoro-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		422 [M+H] ⁺
65	3-Chloro-2-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-6-fluoro-benzoic acid		466 [M+H] ⁺

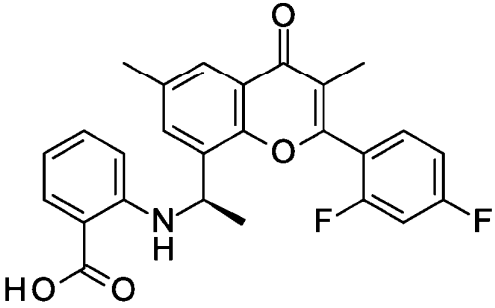
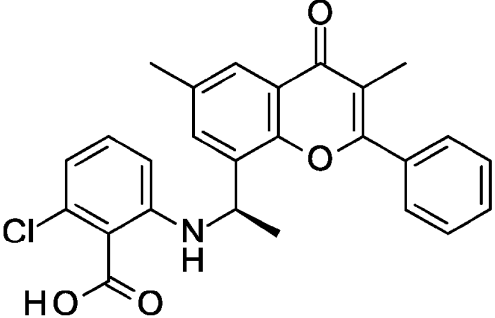
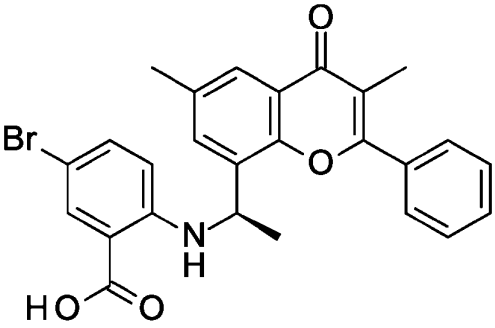
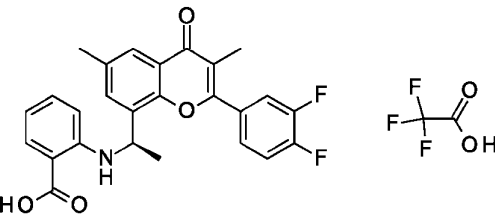
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66	2-[[[(1R)-1-[2-(4-Methoxyphenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		430 [M+H] ⁺
67	2-[[[(1R)-1-[2-(2-Methoxyphenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		430 [M+H] ⁺
68	2-[[[(1R)-1-[2-(3,5-Difluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		436 [M+H] ⁺
69	2-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]-6-fluoro-benzoic acid		432 [M+H] ⁺
70	2-[[[(1R)-1-[6-Methyl-4-oxo-2-phenyl-3-(trifluoromethyl)chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		468 [M+H] ⁺

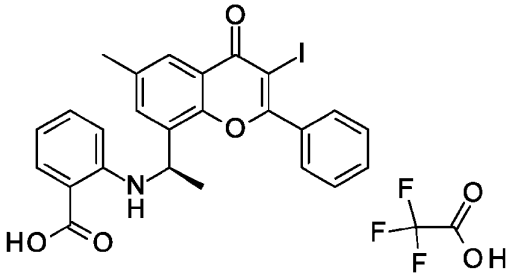
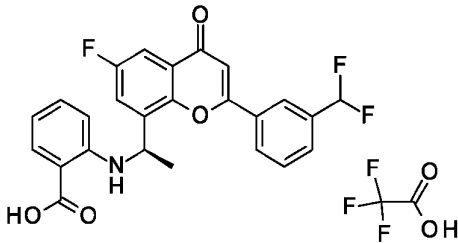
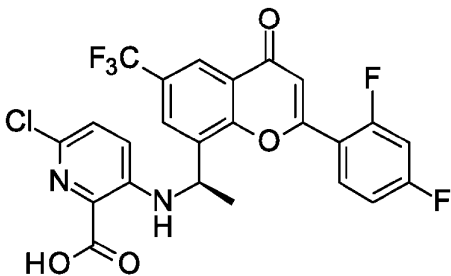
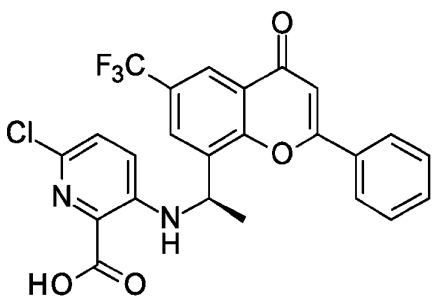
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71	2-[[[(1R)-1-[2-[3-(Difluoromethyl)phenyl]-6-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		450 [M+H] ⁺
72	2-[[[(1R)-1-(6-Fluoro-3-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		418 [M+H] ⁺
73	2-[[[(1R)-1-[2-[3-(Difluoromethyl)phenyl]-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		464 [M+H] ⁺
74	5-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyrimidine-4-carboxylic acid		416 [M+H] ⁺

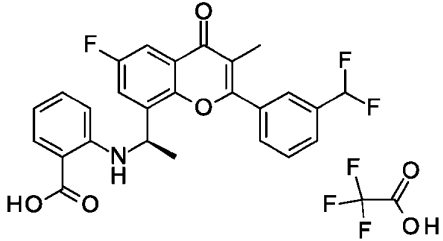
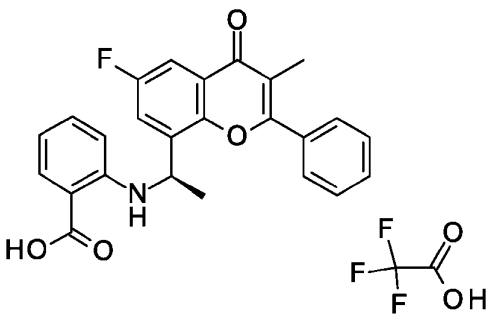
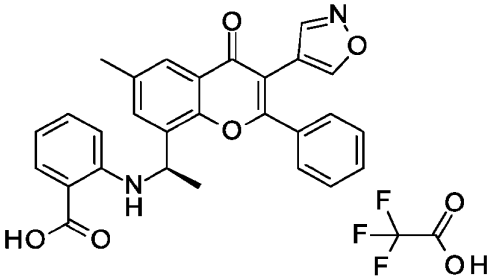
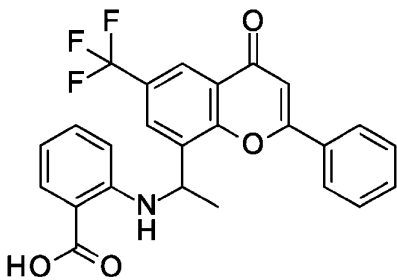
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75	2-[[[(1R)-1-[2-(2,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		450 [M+H] ⁺
76	2-Chloro-6-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		448 [M+H] ⁺
77	5-Bromo-2-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid		494 [M+H] ⁺
78	2-[[[(1R)-1-[2-(3,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		450 [M+H] ⁺

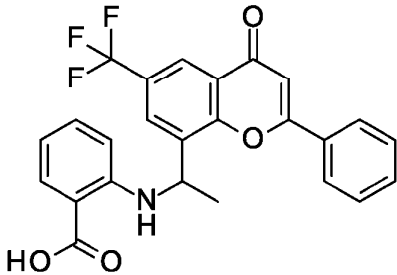
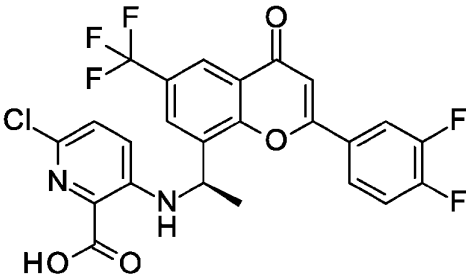
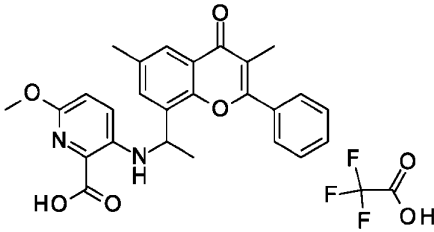
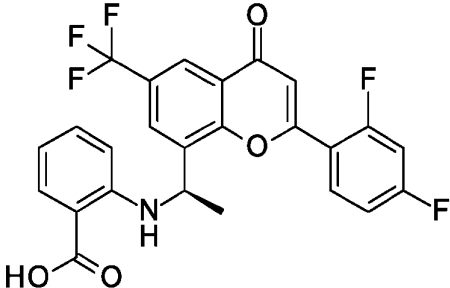
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79	2-[[[(1R)-1-(3-Iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		526 [M+H] ⁺
80	2-[[[(1R)-1-[2-[3-(Difluoromethyl)phenyl]-6-fluoro-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		454 [M+H] ⁺
81	6-Chloro-3-[[[(1R)-1-[2-(2,4-difluorophenyl)-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		525 [M+H] ⁺
82	6-Chloro-3-[[[(1R)-1-[4-oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		489 [M+H] ⁺

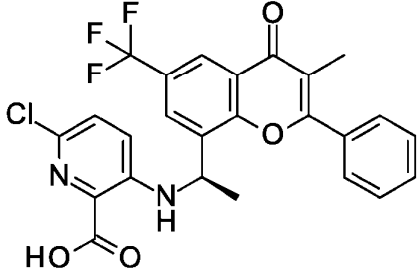
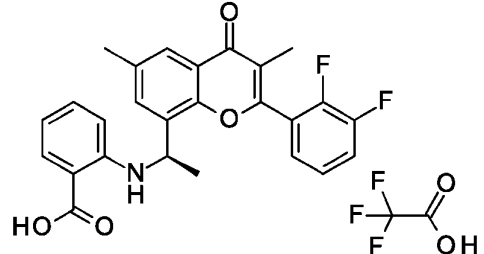
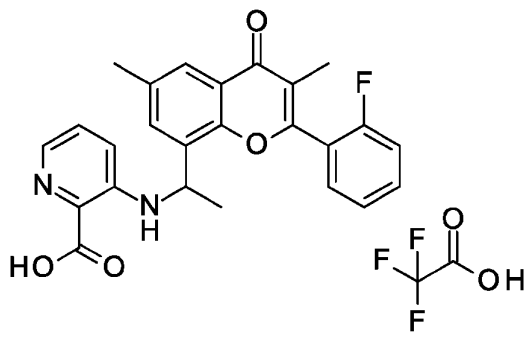
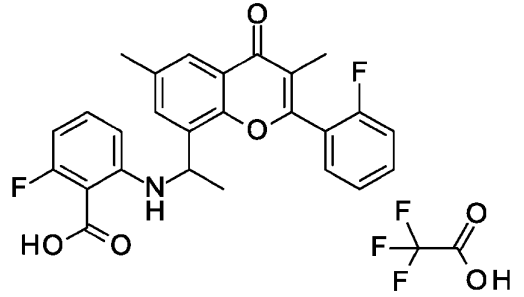
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83	2-[[[(1R)-1-[2-[3-(Difluoromethyl)phenyl]-6-fluoro-3-methyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		468 [M+H] ⁺
84	2-[[[(1R)-1-(6-Fluoro-3-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		418 [M+H] ⁺
85	2-[[[(1R)-1-(3-Isoxazol-4-yl-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		467 [M+H] ⁺
86	2-[1-[4-Oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethylamino]benzoic acid, Isomer 1		454 [M+H] ⁺

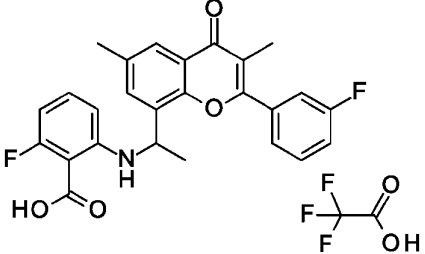
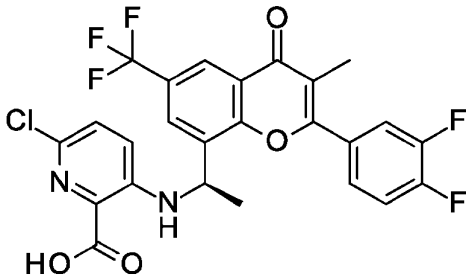
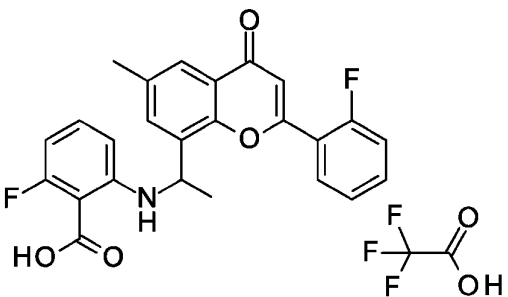
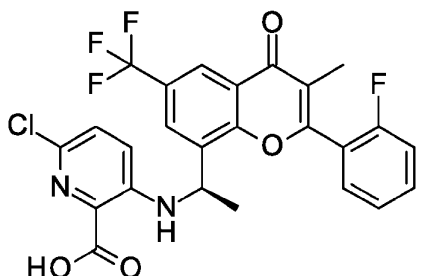
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87	2-[1-[4-Oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethylamino]benzoic acid, Isomer 2		454 [M+H] ⁺
88	6-Chloro-3-[[[(1R)-1-[2-(3,4-difluorophenyl)-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		525 [M+H] ⁺
89	3-[1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]-6-methoxy-pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		445 [M+H] ⁺
90	2-[[[(1R)-1-[2-(2,4-Difluorophenyl)-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]benzoic acid		490 [M+H] ⁺

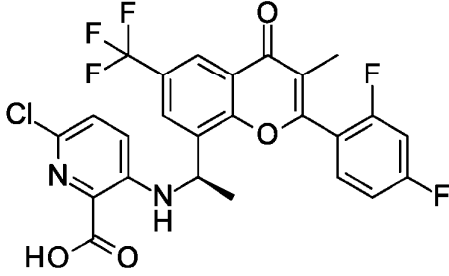
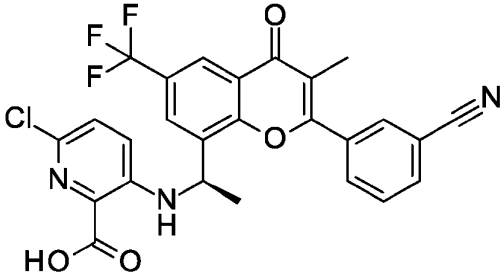
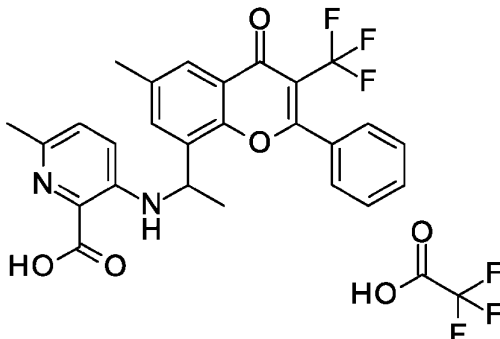
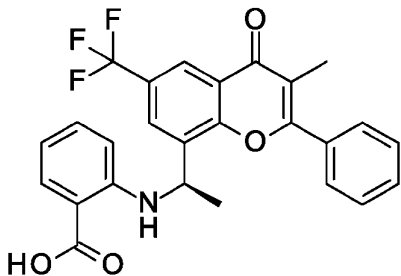
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91	6-Chloro-3-[[[(1R)-1-[3-methyl-4-oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		503 [M+H] ⁺
92	2-[[[(1R)-1-[2-(2,3-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		450 [M+H] ⁺
93	3-[1-[2-(2-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		433 [M+H] ⁺
94	2-Fluoro-6-[1-[2-(2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		450 [M+H] ⁺

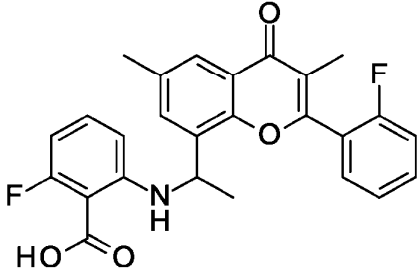
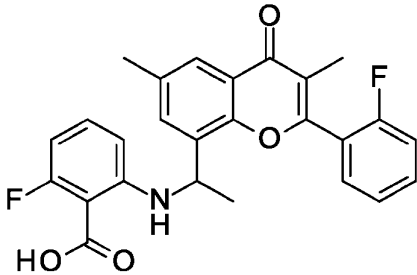
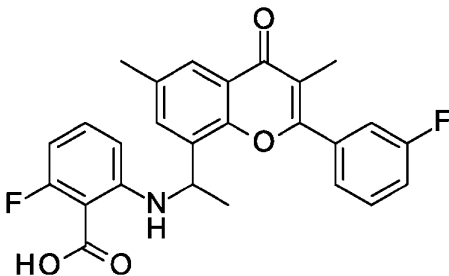
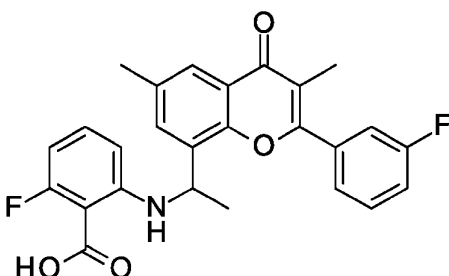
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95	2-Fluoro-6-[1-[2-(3-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		450 [M+H] ⁺
96	6-Chloro-3-[[[(1R)-1-[2-(3,4-difluorophenyl)-3-methyl-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		539 [M+H] ⁺
97	2-Fluoro-6-[1-[2-(2-fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		436 [M+H] ⁺
98	6-Chloro-3-[[[(1R)-1-[2-(2-fluorophenyl)-3-methyl-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		521 [M+H] ⁺

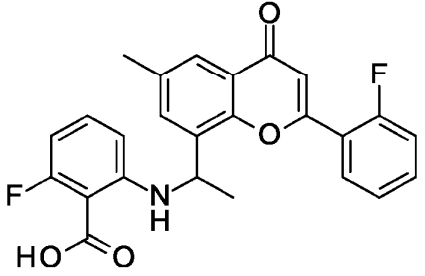
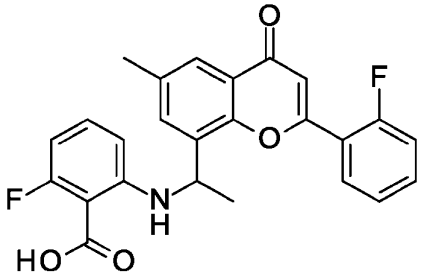
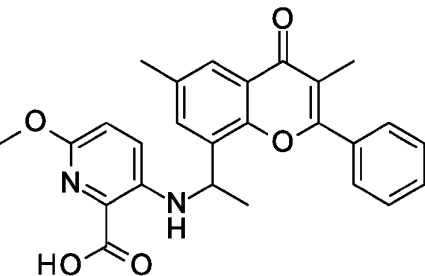
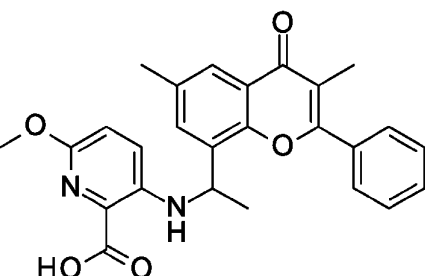
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99	6-Chloro-3-[[[(1R)-1-[2-(2,4-difluorophenyl)-3-methyl-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		539 [M+H] ⁺
100	6-Chloro-3-[[[(1R)-1-[2-(3-cyanophenyl)-3-methyl-4-oxo-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		528 [M+H] ⁺
101	6-Methyl-3-[1-[6-methyl-4-oxo-2-phenyl-3-(trifluoromethyl)chromen-8-yl]ethylamino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		483 [M+H] ⁺
102	2-[[[(1R)-1-[3-Methyl-4-oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]benzoic acid		468 [M+H] ⁺

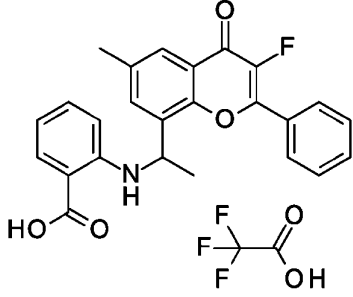
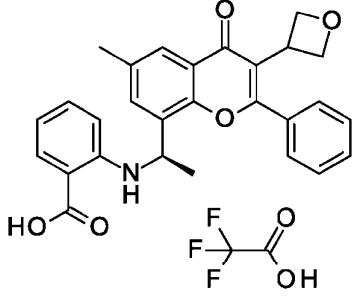
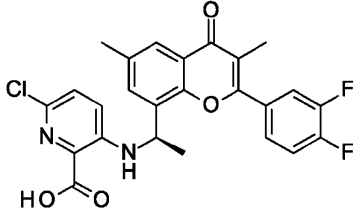
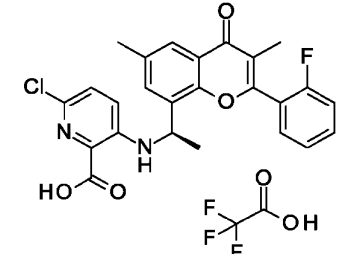
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103	2-Fluoro-6-[1-[2-(2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		450 [M+H] ⁺
104	2-Fluoro-6-[1-[2-(2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		450 [M+H] ⁺
105	2-Fluoro-6-[1-[2-(3-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		450 [M+H] ⁺
106	2-Fluoro-6-[1-[2-(3-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		450 [M+H] ⁺

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107	2-Fluoro-6-[1-[2-(2-fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 1		436 [M+H] ⁺
108	2-Fluoro-6-[1-[2-(2-fluorophenyl)-6-methyl-4-oxo-chromen-8-yl]ethylamino]benzoic acid, Isomer 2		436 [M+H] ⁺
109	3-[1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]-6-methoxy-pyridine-2-carboxylic acid, Isomer 1		445 [M+H] ⁺
110	3-[1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]-6-methoxy-pyridine-2-carboxylic acid, Isomer 2		445 [M+H] ⁺

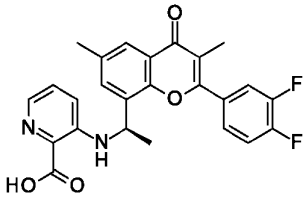
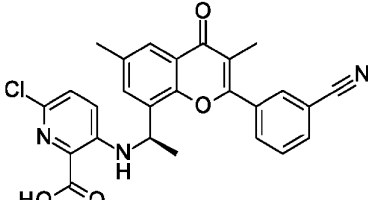
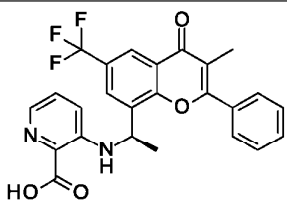
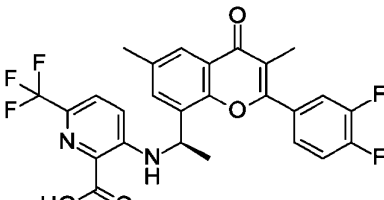
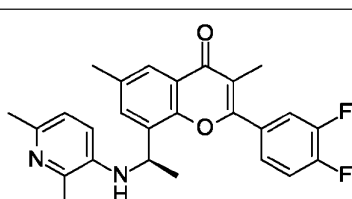
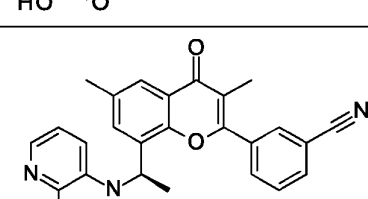
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111	2-[1-(3-Fluoro-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid 2,2,2-trifluoroacetic acid		418 [M+H] ⁺
112	2-[[[(1R)-1-[6-methyl-3-(oxetan-3-yl)-4-oxo-2-phenyl-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		456 [M+H] ⁺
113	6-Chloro-3-[[[(1R)-1-[2-(3,4-difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		
114	6-Chloro-3-[[[(1R)-1-[2-(2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		467 [M+H] ⁺

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115	6-Chloro-3-[[[(1R)-1-[2-(3-cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		474 [M+H] ⁺
116	6-Methyl-3-[[[(1R)-1-[6-methyl-4-oxo-2-phenyl-3-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		483 [M+H] ⁺
117	2-[[[(1R)-1-[2-[3-(1-Cyano-1-methyl-ethyl)phenyl]-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		481 [M+H] ⁺
118	2-[[[(1R)-1-[2-[3-(2-Amino-1,1-dimethyl-2-oxo-ethyl)phenyl]-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		499 [M+H] ⁺
119	2-[[[(1R)-1-(3-Acetyl-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		442 [M+H] ⁺

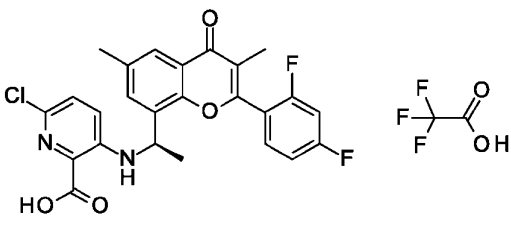
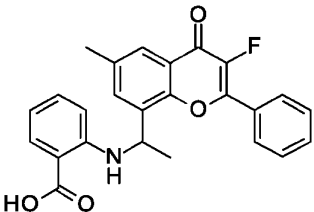
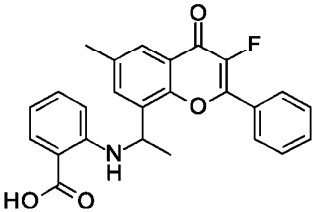
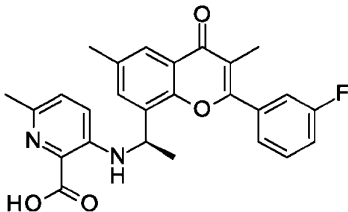
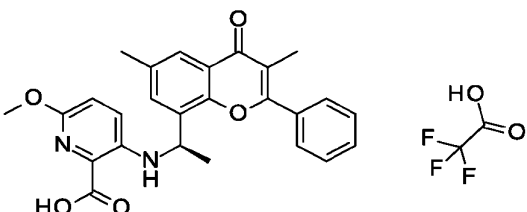
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120	3-[[[(1R)-1-[2-(3,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		451 [M+H] ⁺
121	6-Chloro-3-[[[(1R)-1-[2-(3-cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		474 [M+H] ⁺
122	3-[[[(1R)-1-[3-Methyl-4-oxo-2-phenyl-6-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		469 [M+H] ⁺
123	3-[[[(1R)-1-[2-(3,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-(trifluoromethyl)pyridine-2-carboxylic acid		519 [M+H] ⁺
124	3-[[[(1R)-1-[2-(3,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-methyl-pyridine-2-carboxylic acid		465 [M+H] ⁺
125	3-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		440 [M+H] ⁺

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126	3-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-(trifluoromethyl)pyridine-2-carboxylic acid		508 [M+H] ⁺
127	3-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-methyl-pyridine-2-carboxylic acid		454 [M+H] ⁺
128	2-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-5-(trifluoromethyl)benzoic acid		507 [M+H] ⁺
129	2-[[[(1R)-1-[2-(3-Cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-5-fluoro-benzoic acid		457 [M+H] ⁺
130	2-[[[(1R)-1-[2-(2,4-Difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-fluoro-benzoic acid 2,2,2-trifluoroacetic acid		468 [M+H] ⁺

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131	6-Chloro-3-[[[(1R)-1-[2-(2,4-difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		485 [M+H] ⁺
132	2-[1-(3-Fluoro-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid, Isomer 1		418 [M+H] ⁺
133	2-[1-(3-Fluoro-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]benzoic acid, Isomer 2		418 [M+H] ⁺
134	3-[[[(1R)-1-[2-(3-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-methyl-pyridine-2-carboxylic acid		447 [M+H] ⁺
135	6-Methoxy-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		445 [M+H] ⁺

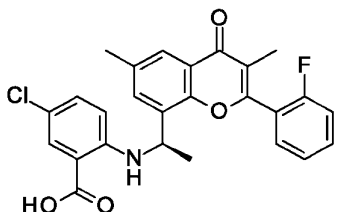
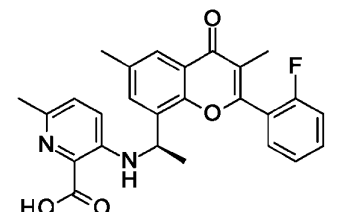
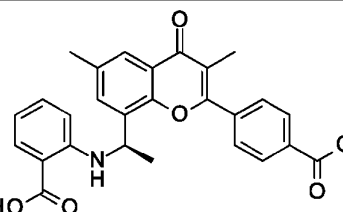
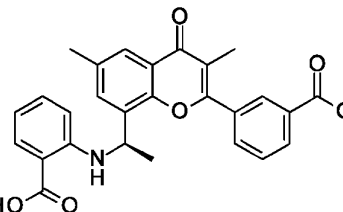
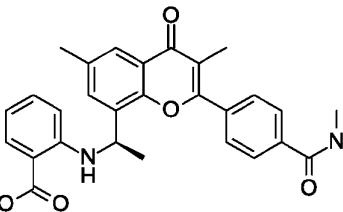
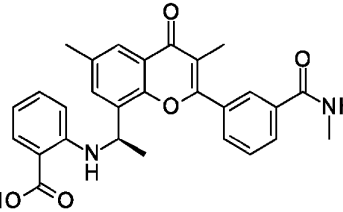
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136	3-[[[(1R)-1-[2-(3-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		433 [M+H] ⁺
137	2-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-3-carboxylic acid		415 [M+H] ⁺
138	3-[[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-4-carboxylic acid		415 [M+H] ⁺
139	6-Chloro-3-[[[(1R)-1-[6-methyl-4-oxo-2-phenyl-3-(trifluoromethyl)chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		503 [M+H] ⁺
140	6-Chloro-3-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]pyridine-2-carboxylic acid 2,2,2-trifluoroacetic acid		561 [M+H] ⁺

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141	6-Bromo-3-[[[(1R)-1-[2-(3-cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		520 [M+H] ⁺
142	3-[[[(1R)-1-[2-(2-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]pyridine-2-carboxylic acid		433 [M+H] ⁺
143	2-Fluoro-6-[[[(1R)-1-[2-(3-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		450 [M+H] ⁺
144	5-Chloro-2-[[[(1R)-1-[2-(3-cyanophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		473 [M+H] ⁺
145	5-Chloro-2-[[[(1R)-1-[2-(3-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		466 [M+H] ⁺
146	5-Chloro-2-[[[(1R)-1-[2-(3,4-difluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		484 [M+H] ⁺

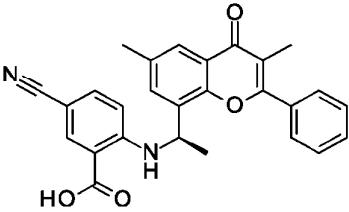
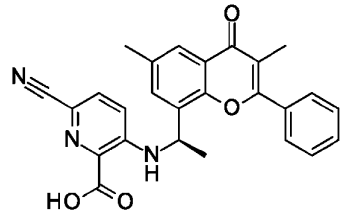
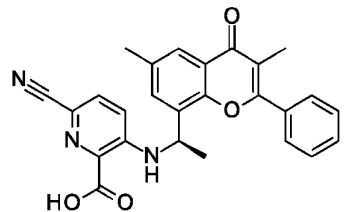
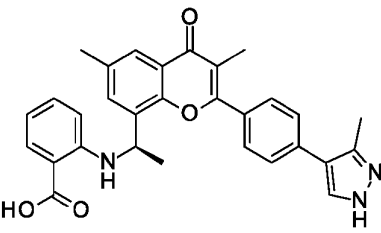
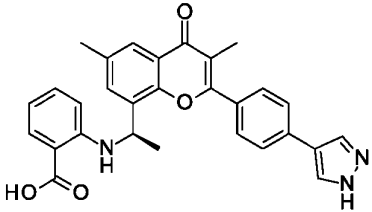
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147	5-Chloro-2-[[[(1R)-1-[2-(2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		466 [M+H] ⁺
148	3-[[[(1R)-1-[2-(2-Fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]-6-methyl-pyridine-2-carboxylic acid		447 [M+H] ⁺
149	2-[[[(1R)-1-[2-(4-Methoxycarbonylphenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		472 [M+H] ⁺
150	2-[[[(1R)-1-[2-(3-Methoxycarbonylphenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		472 [M+H] ⁺
151	2-[[[(1R)-1-[3,6-Dimethyl-2-[4-(methylcarbamoyl)phenyl]-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		471 [M+H] ⁺
152	2-[[[(1R)-1-[3,6-Dimethyl-2-[3-(methylcarbamoyl)phenyl]-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		471 [M+H] ⁺

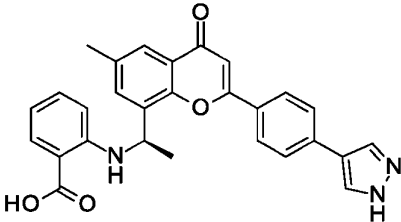
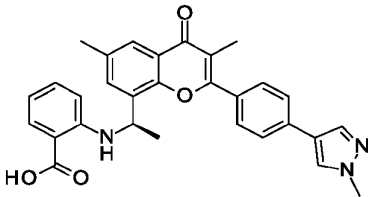
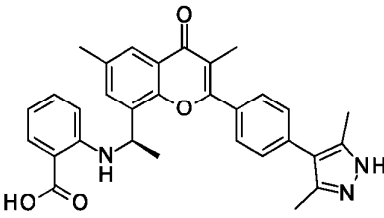
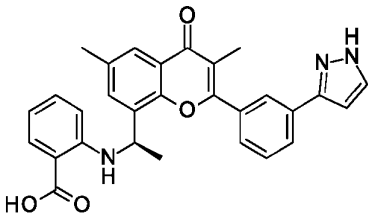
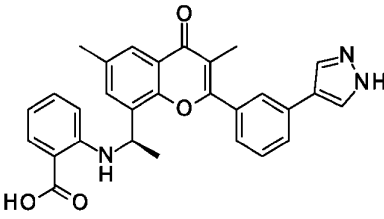
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153	6-Chloro-3-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]pyridine-2-carboxylic acid, Isomer 1		561 [M+H] ⁺
154	6-Chloro-3-[1-(3-iodo-6-methyl-4-oxo-2-phenyl-chromen-8-yl)ethylamino]pyridine-2-carboxylic acid, Isomer 2		561 [M+H] ⁺
155	2-Methoxy-5-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyrimidine-4-carboxylic acid 2,2,2-trifluoroacetic acid		446 [M+H] ⁺
156	2-[[[(1R)-1-[6-Methyl-4-oxo-2-phenyl-3-(3-pyridyl)chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		477 [M+H] ⁺
157	5-Cyano-2-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, Isomer 1		439 [M+H] ⁺

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158	5-Cyano-2-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, Isomer 2		439 [M+H] ⁺
159	6-Cyano-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid, Isomer 1		440 [M+H] ⁺
160	6-Cyano-3-[[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]pyridine-2-carboxylic acid, Isomer 2		440 [M+H] ⁺
161	2-[[[(1R)-1-[3,6-Dimethyl-2-[4-(3-methyl-1H-pyrazol-4-yl)phenyl]-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		494 [M+H] ⁺
162	2-[[[(1R)-1-[3,6-Dimethyl-4-oxo-2-[4-(1H-pyrazol-4-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		480 [M+H] ⁺

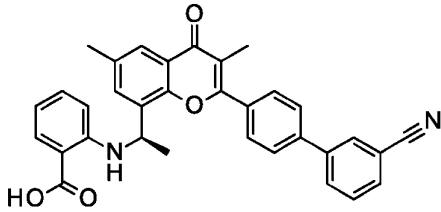
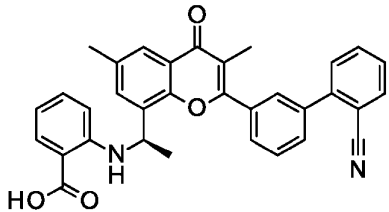
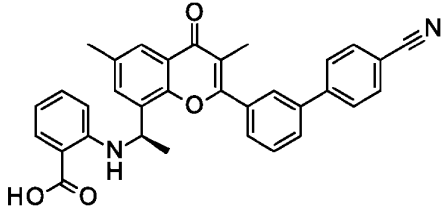
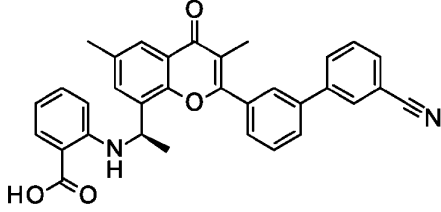
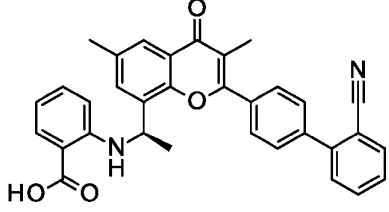
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163	2-[[[(1R)-1-[6-Methyl-4-oxo-2-[4-(1H-pyrazol-4-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		466 [M+H] ⁺
164	2-[[[(1R)-1-[3,6-Dimethyl-2-[4-(1-methylpyrazol-4-yl)phenyl]-4-oxochromen-8-yl]ethyl]amino]benzoic acid		494 [M+H] ⁺
165	2-[[[(1R)-1-[2-[4-(3,5-Dimethyl-1H-pyrazol-4-yl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		508 [M+H] ⁺
166	2-[[[(1R)-1-[3,6-Dimethyl-4-oxo-2-[3-(1H-pyrazol-3-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		480 [M+H] ⁺
167	2-[[[(1R)-1-[3,6-Dimethyl-4-oxo-2-[3-(1H-pyrazol-4-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		480 [M+H] ⁺

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168	2-[[[(1R)-1-[3,6-Dimethyl-4-oxo-2-[4-(1H-pyrazol-5-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		480 [M+H] ⁺
169	2-[[[(1R)-1-[3,6-Dimethyl-4-oxo-2-[4-(1H-pyrazol-5-yl)phenyl]chromen-8-yl]ethyl]amino]benzoic acid		494 [M+H] ⁺
170	2-[[[(1R)-1-[2-(3-Cyano-2-fluorophenyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		457 [M+H] ⁺
171	2-[[[(1R)-1-[3-(2-Carboxyethylamino)-6-methyl-4-oxo-2-phenyl-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		487 [M+H] ⁺
172	2-[[[(1R)-1-[2-[4-(4-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺

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173	2-[[[(1R)-1-[2-[4-(3-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺
174	2-[[[(1R)-1-[2-[3-(2-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺
175	2-[[[(1R)-1-[2-[3-(4-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺
176	2-[[[(1R)-1-[2-[3-(3-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺
177	2-[[[(1R)-1-[2-[4-(2-Cyanophenyl)phenyl]-3,6-dimethyl-4-oxochromen-8-yl]ethyl]amino]benzoic acid		515 [M+H] ⁺

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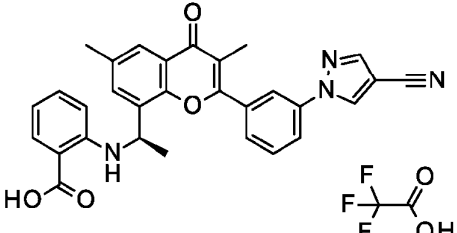
178	2-[[[(1R)-1-[2-[3-(4-Cyanopyrazol-1-yl)phenyl]-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid 2,2,2-trifluoroacetic acid		505 [M+H] ⁺
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Table 2:

Ex #	NMR Line Listing
1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.58 (d, J=6.8 Hz, 3H), 2.07 (s, 3H), 2.36 (s, 3H), 5.09-5.11 (m, 1H), 6.95 (d, J=8.2 Hz, 1H), 7.19 (d, J=8.8 Hz, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.58-7.59 (m, 3H), 7.78-7.81 (m, 3H), 8.72 (s, 1H)
2	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.4 Hz, 3H), 2.34 (s, 3H), 5.20-5.23 (m, 1H), 6.74 (d, J=8.4 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 7.07 (s, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.57-7.62 (m, 3H), 7.73 (s, 1H), 8.13 (dd, J=8.0, 2.0 Hz, 2H), 9.88 (s, 1H)
3	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.66 - 1.74 (m, 3H), 1.77 (br s, 6H), 2.37 (br s, 3H), 5.26 - 5.44 (m, 1H), 6.47 - 6.62 (m, 2H), 7.18 - 7.28 (m, 2H), 7.55 (br s, 1H), 7.63 - 7.71 (m, 1H), 7.74 - 7.86 (m, 3H), 8.09 - 8.18 (m, 1H), 8.25 (br s, 1H), 8.41 - 8.50 (m, 1H), 12.65 - 12.99 (m, 1H)
5	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.71 (br d, J=5.26 Hz, 3H), 1.77 (br s, 6H), 2.29 - 2.44 (m, 4H), 5.34 (br s, 1H), 6.49 - 6.57 (m, 2H), 7.22 (br s, 2H), 7.55 (br s, 1H), 7.64 - 7.69 (m, 1H), 7.77 (br s, 1H), 7.82 (br d, J=8.56 Hz, 1H), 8.13 (br d, J=7.46 Hz, 1H), 8.25 (br s, 1H), 8.45 (br s, 1H), 12.61 - 12.94 (m, 1H)
6	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.90 (br d, J=5.4 Hz, 3H), 5.56 (br d, J=4.8 Hz, 1H), 6.52 - 6.65 (m, 1H), 6.66 - 6.78 (m, 1H), 7.05 (s, 1H), 7.20 - 7.33 (m, 1H), 7.55 - 7.72 (m, 3H), 7.85 - 7.98 (m, 2H), 8.11 - 8.22 (m, 2H)
7	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 - 1.72 (m, 5H), 1.88 (br s, 2H), 2.37 (br s, 3H), 5.33 (br s, 1H), 6.52 (br d, J=8.68 Hz, 1H), 6.57 (br s, 1H), 7.11 (br s, 1H), 7.19 - 7.26 (m, 1H), 7.52 (br d, J=7.95 Hz, 2H), 7.56 (br s, 1H), 7.76 (br s, 1H), 7.83 (br d, J=7.58 Hz, 1H), 8.16 (br d, J=7.46 Hz, 2H), 8.44 (br s, 1H), 12.79 (br s, 1H)
8	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.63 - 1.74 (m, 3H), 2.37 (s, 3H), 2.93 (s, 3H), 3.02 (s, 3H), 5.35 (s, 1H), 6.51 - 6.57 (m, 2H), 7.15 (s, 1H), 7.20 - 7.26 (m, 1H), 7.56 - 7.62 (m, 3H), 7.77 (s, 1H), 7.82 (d, J=7.7 Hz, 1H), 8.19 (d, J=7.5 Hz, 2H), 8.45 (s, 1H), 12.81 (s, 1H)
9	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.64 - 1.72 (m, 3H), 2.38 (s, 3H), 3.32-3.40 (m, 4H), 5.35 (s, 1H), 6.51 - 6.58 (m, 2H), 7.21 - 7.29 (m, 2H), 7.60 (s, 1H), 7.77 (s, 1H), 7.83 (d, J=7.4 Hz, 1H), 8.11 (d, J=7.8 Hz, 2H), 8.41 (d, J=7.7 Hz, 2H), 12.83

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	(s, 1H)
10	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.63 (bs, 3H), 2.40 (bs, 3H), 5.19 (bs, 1H), 6.50 (d, J=7.70 Hz, 1H), 6.56-6.59 (m, 1H), 7.19-7.23 (m, 1H), 7.64 (bs, 1H), 7.69-7.73 (m, 2H), 7.76 (d, J=4.4 Hz, 1H), 7.83 (m, 2H), 8.14 (bd, J=6.9 Hz, 2H), 8.38 (bs, 1H), 12.75 (bs, 1H)
11	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.62 (d, J=6.8 Hz, 3H), 2.36 (s, 3H), 5.23-5.25 (m, 1H), 6.44 (d, J=8.4 Hz, 1H), 6.53 (t, J=7.6 Hz, 1H), 6.84 (s, 1H), 7.15-7.20 (m, 1H), 7.44-7.55 (m, 2H), 7.56 (d, J=2.0 Hz, 1H), 7.65-7.69 (m, 1H), 7.75 (s, 1H), 7.81 (d, J=8.0 Hz, 1H), 8.04-8.05 (m, 1H), 8.57 (s, 1H)
12	¹ H NMR (400 MHz, DMSO-d6) δ ppm 0.87 (br s, 2H) 0.91 - 1.01 (m, 2H) 1.44 (br s, 3H) 1.63 - 1.74 (m, 3H) 2.37 (br s, 3H) 5.27 - 5.37 (m, 1H) 6.49 - 6.60 (m, 2H) 7.02 - 7.09 (m, 1H) 7.18 - 7.28 (m, 1H) 7.36 - 7.46 (m, 2H) 7.53 - 7.61 (m, 1H) 7.73 - 7.78 (m, 1H) 7.79 - 7.86 (m, 1H) 8.00 - 8.09 (m, 2H) 8.40 - 8.49 (m, 1H) 12.68 - 12.96 (m, 1H)
13	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.72 (br d, J=3.6 Hz, 3H), 2.38 (br s, 3H), 3.83 - 3.94 (m, 3H), 5.42 (s, 1H), 6.51 - 6.63 (m, 2H), 7.18 - 7.31 (m, 2H), 7.53 - 7.63 (m, 2H), 7.75 - 7.89 (m, 3H), 7.90 - 8.00 (m, 1H), 8.00 - 8.10 (m, 1H), 8.24 - 8.38 (m, 2H), 8.41 - 8.55 (m, 1H), 12.65 - 12.96 (m, 1H)
14	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.56 (d, J=6.4 Hz, 3H), 2.36 (s, 3H), 2.50 (s, 3H), 5.13-5.15 (m, 1H), 6.38 (d, J=8.4 Hz, 1H), 6.52-6.56 (m, 2H), 7.16-7.18 (m, 1H), 7.40-7.41 (m, 2H), 7.46-7.49 (m, 1H), 7.55 (s, 1H), 7.67 (d, J=7.2 Hz, 1H), 7.78-7.82 (m, 2H), 8.37 (d, J=4.0 Hz, 1H)
15	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.53 (d, J=5.6 Hz, 3H), 2.34 (s, 3H), 5.27-5.29 (m, 1H), 6.34-6.38 (m, 3H), 6.87 (t, J=7.2 Hz, 1H), 6.92 (s, 1H), 7.59 (s, 1H), 7.75 (s, 1H), 7.82 (t, J=7.6 Hz, 1H), 7.94 (t, J=7.6 Hz, 1H), 8.11-8.14 (m, 2H), 9.84 (s, 1H)
16	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.65 (d, J=6.8 Hz, 3H), 2.36 (s, 3H), 5.38-5.39 (m, 1H), 6.50-6.55 (m, 2H), 7.16-7.20 (m, 1H), 7.24 (s, 1H), 7.57 (d, J=2.0 Hz, 1H), 7.75 (s, 1H), 7.77-7.81 (m, 2H), 8.07-8.08 (m, 2H), 8.45 (d, J=8.4 Hz, 1H), 8.61 (s, 1H)
17	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.66 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.32-5.35 (m, 1H), 6.51-6.57 (m, 2H), 7.22-7.25 (m, 2H), 7.58 (d, J=2.0 Hz, 1H), 7.76 (s, 1H), 7.81 (d, J=8.0 Hz, 1H), 8.04-8.06 (m, 2H), 8.31-8.33 (m, 2H), 8.45 (s, 1H), 12.79 (s, 1H)
18	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.67 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.34-5.35 (m, 1H), 6.50-6.57 (m, 2H), 7.18-7.22 (m, 2H), 7.43-7.48 (m, 1H), 7.57 (d, J=2.0 Hz, 1H), 7.62-7.64 (m, 1H), 7.75 (s, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.97-8.01 (m, 2H), 8.55 (s, 1H), 12.84 (br s, 1H)
19	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.66 (d, J=6.0 Hz, 3H), 2.36 (s, 3H), 5.32-5.33 (m, 1H), 6.50-6.57 (m, 2H), 7.08 (s, 1H), 7.21 (t, J=7.6 Hz, 1H), 7.42 (t, J=8.8 Hz, 2H), 7.56 (s, 1H), 7.74 (s, 1H), 7.82 (d, J=8.0 Hz, 1H), 8.19-8.22 (m, 2H), 8.47 (s, 1H), 12.83 (br s, 1H)

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20	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.67 (d, J=6.4 Hz, 3H), 2.36 (s, 3H), 5.31-5.32 (m, 1H), 6.51-6.52 (m, 1H), 7.09 (s, 1H), 7.11-7.14 (m, 1H), 7.52-7.54 (m, 2H), 7.57-7.62 (m, 3H), 7.75 (s, 1H), 8.13-8.14 (m, 2H), 8.29 (s, 1H), 13.15 (br s, 1H)
21	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.58 (d, J=6.8 Hz, 3H), 2.09 (s, 3H), 2.36 (s, 3H), 5.10-5.13 (m, 1H), 6.44 (d, J=8.8 Hz, 1H), 6.54 (t, J=7.6 Hz, 1H), 7.19-7.21 (m, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.58-7.60 (m, 3H), 7.79-7.82 (m, 4H), 8.39 (s, 1H), 12.74 (br s, 1H)
22	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.68 (d, J=6.8 Hz, 3H), 2.36 (s, 3H), 5.32-5.35 (m, 1H), 6.51-6.57 (m, 2H), 7.08 (s, 1H), 7.19-7.24 (m, 1H), 7.56-7.60 (m, 4H), 7.75 (s, 1H), 7.82 (d, J=7.6 Hz, 1H), 8.13 (d, J=7.6 Hz, 2H), 8.45 (d, J=5.2 Hz, 1H), 12.88 (br s, 1H)
23	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.72 (d, J=6.72 Hz, 3H), 2.33 (s, 3H), 2.41 (s, 3H), 5.07 - 5.16 (m, 1H), 7.08 (s, 1H), 7.57 - 7.64 (m, 3H), 7.66 (d, J=2.08 Hz, 1H), 7.80 (d, J=1.34 Hz, 1H), 7.95 (d, J=6.72 Hz, 1H), 8.12 (dd, J=7.95, 1.59 Hz, 2H), 12.17 (br s, 1H)
24	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.70 (d, J=6.8 Hz, 3H), 5.36-5.39 (m, 1H), 6.51 (d, J=8.4 Hz, 1H), 6.58 (t, J=7.6 Hz, 1H), 7.15 (s, 1H), 7.20-7.24 (m, 1H), 7.53 (dd, J=8.8, 3.2 Hz, 1H), 7.60-7.64 (m, 4H), 7.83 (d, J=8.0 Hz, 1H), 8.14-8.16 (m, 2H), 8.44 (s, 1H), 12.73 (s, 1H)
25	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.68 (br d, J=6.60 Hz, 3H), 1.75 (s, 6H), 2.37 (s, 3H), 5.30 - 5.39 (m, 1H), 6.50 - 6.60 (m, 2H), 7.13 (s, 1H), 7.23 (t, J=7.04 Hz, 1H), 7.52 - 7.61 (m, 1H), 7.71 - 7.79 (m, 3H), 7.83 (d, J=7.24 Hz, 1H), 8.21 (d, J=8.44 Hz, 2H), 8.45 (br d, J=5.99 Hz, 1H), 12.80 (br s, 1H)
26	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.63 (d, J=6.8 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.17-5.24 (m, 1H), 7.02-7.07 (m, 1H), 7.56-7.58 (m, 4H), 7.63 (d, J=8.8 Hz, 1H), 7.78-7.80 (m, 3H), 8.63 (d, J=6.4 Hz, 1H), 13.32 (s, 1H)
27	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.72 (d, J=6.4 Hz, 3H), 2.36 (s, 3H), 5.39-5.46 (m, 1H), 7.09 (s, 1H), 7.16 (d, J=9.2 Hz, 1H), 7.56-7.62 (m, 4H), 7.66 (d, J=9.2 Hz, 1H), 7.77 (s, 1H), 8.13 (d, J=6.8 Hz, 2H), 8.75 (d, J=6.0 Hz, 1H)
28	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.58 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.11-5.14 (m, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.54 (t, J=7.6 Hz, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.42-7.48 (m, 1H), 7.53 (s, 1H), 7.66-7.69 (m, 3H), 7.78-7.82 (m, 2H), 8.36-8.37 (m, 1H)
29	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.58 (d, J=6.8 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 5.10-5.13 (m, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.55 (t, J=7.2 Hz, 1H), 7.20 (t, J=6.8 Hz, 1H), 7.41-7.46 (m, 2H), 7.53 (d, J=2.0 Hz, 1H), 7.78-7.80 (m, 2H), 7.86-7.90 (m, 2H), 8.37-8.38 (m, 1H)
30	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.58 (d, J=6.0 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 5.13-5.15 (m, 1H), 6.47 (d, J=8.4 Hz, 1H), 6.53 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.54 (s, 1H), 7.79-7.83 (m, 3H), 8.07 (d, J=7.6 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H), 8.30 (s, 1H), 8.39 (s, 1H)

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31	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.56 (d, J=6.8 Hz, 3H), 2.06 (s, 3H), 2.36 (s, 3H), 5.08-5.10 (m, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.53 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 7.54 (d, J=2.0 Hz, 1H), 7.77-7.80 (m, 2H), 7.98-8.00 (m, 2H), 8.05-8.07 (m, 2H), 8.38 (s, 1H)
32	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.69 (d, J=6.4 Hz, 3H), 2.37 (s, 3H), 5.34-5.37 (m, 1H), 6.54-6.58 (m, 2H), 7.16 (s, 1H), 7.24 (t, J=7.6 Hz, 1H), 7.47 (s, 1H), 7.59 (s, 1H), 7.76 (s, 1H), 7.82 (d, J=7.6 Hz, 1H), 8.15 (d, J=8.4 Hz, 2H), 8.28-8.31 (m, 3H), 8.43 (d, J=6.0 Hz, 1H), 12.79 (s, 1H)
33	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.71 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.41-5.46 (m, 1H), 6.72 (d, J=9.2 Hz, 1H), 7.09 (s, 1H), 7.53-7.60 (m, 5H), 7.72 (s, 1H), 8.06 (s, 1H), 8.11-8.13 (m, 2H), 8.82 (d, J=6.4 Hz, 1H), 13.43 (s, 1H)
34	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54 (d, J=6.8 Hz, 3H), 1.92 (s, 3H), 2.37 (s, 3H), 5.07-5.10 (m, 1H), 6.42 (d, J=8.4 Hz, 1H), 6.51 (t, J=7.6 Hz, 1H), 7.13 (t, J=6.8 Hz, 1H), 7.54 (s, 1H), 7.77-7.84 (m, 3H), 7.94-7.95 (m, 2H), 8.13 (d, J=7.6 Hz, 1H), 8.37 (s, 1H)
35	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.60 (d, J=6.8 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.10-5.17 (m, 1H), 6.95 (d, J=8.8 Hz, 1H), 7.38 (d, J=9.2 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.58-7.59 (m, 3H), 7.77-7.79 (m, 3H), 8.30 (d, J=6.4 Hz, 1H), 13.08 (s, 1H)
36	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 (d, J=6.8 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.14-5.17 (m, 1H), 7.08 (d, J=8.4 Hz, 1H), 7.30-7.34 (m, 1H), 7.54 (s, 1H), 7.58-7.60 (m, 3H), 7.79-7.84 (m, 4H), 8.64 (d, J=6.4 Hz, 1H)
37	¹ H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.70 (d, J=6.8 Hz, 3H), 2.22 (s, 3H), 2.42 (s, 3H), 5.19-5.23 (m, 1H), 6.46 (d, J=8.8 Hz, 1H), 7.40-7.44 (m, 2H), 7.54-7.56 (m, 3H), 7.66-7.68 (m, 2H), 7.98 (s, 1H), 8.26 (s, 1H), 8.44 (d, J=6.0 Hz, 1H)
38	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.56 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.04-5.06 (m, 1H), 6.18-6.21 (m, 1H), 7.22-7.26 (m, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.58-7.60 (m, 3H), 7.78-7.80 (m, 3H), 7.86 (s, 1H)
39	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.56 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.35-2.37 (m, 6H), 5.04-5.06 (m, 1H), 6.18-6.21 (m, 1H), 7.22-7.26 (m, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.58-7.60 (m, 3H), 7.78-7.80 (m, 3H), 7.86 (s, 1H)
40	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 0.82-0.84 (m, 4H), 1.58 (d, J=6.8 Hz, 3H), 1.94-2.00 (m, 1H), 2.07 (s, 3H), 2.36 (s, 3H), 5.11-5.15 (m, 1H), 6.93 (d, J=8.8 Hz, 1H), 7.12 (d, J=8.8 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.58-7.59 (m, 3H), 7.78-7.81 (m, 3H), 8.10 (d, J=6.4 Hz, 1H)
41	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.58 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.09-5.12 (m, 1H), 6.48 (d, J=9.2 Hz, 1H), 7.23 (dd, J=8.8, 2.4 Hz, 1H), 7.51 (s, 1H), 7.58-7.60 (m, 3H), 7.74 (d, J=2.8 Hz, 1H), 7.79-7.80 (m, 3H), 8.34 (s, 1H), 13.17 (s, 1H)
42	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.05-5.07 (m, 1H), 6.23 (d, J=9.2 Hz, 1H), 7.22 (t, J=8.8 Hz, 1H), 7.51 (d, J=2.4 Hz, 1H), 7.58-7.60 (m, 3H), 7.78-7.80 (m, 3H), 8.10 (s, 1H)

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43	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54 (d, J=6.8 Hz, 3H), 2.01 (s, 3H), 2.08 (s, 3H), 2.36 (s, 3H), 5.04-5.05 (m, 1H), 6.15 (d, J=8.4 Hz, 1H), 7.01 (t, J=8.4 Hz, 1H), 7.05-7.06 (m, 1H), 7.58-7.60 (m, 3H), 7.77-7.80 (m, 4H)
44	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.4 Hz, 3H), 1.92 (s, 3H), 2.36 (s, 3H), 5.02-5.05 (m, 1H), 6.40 (d, J=8.4 Hz, 1H), 6.53 (t, J=7.6 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 7.42-7.50 (m, 2H), 7.53 (s, 1H), 7.62-7.73 (m, 1H), 7.78-7.80 (m, 3H), 8.36 (s, 1H)
45	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.65 (d, J=5.6 Hz, 3H), 1.98 (s, 4H), 2.29 (s, 3H), 4.02 (s, 4H), 5.23 (d, J=5.9 Hz, 1H), 6.29 (d, J=8.5 Hz, 1H), 6.47 - 6.52 (m, 1H), 6.55 (d, J=8.3 Hz, 2H), 6.65 (s, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.31 (s, 1H), 7.43 (s, 1H), 7.72 - 7.80 (m, 3H), 7.90 (d, J=7.8 Hz, 1H)
46	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.69 (d, J=6.8 Hz, 3H), 2.36 (s, 6H), 5.35-5.38 (m, 1H), 7.08-7.10 (m, 2H), 7.23 (d, J=8.8 Hz, 1H), 7.54 (d, J=2.0 Hz, 1H), 7.58-7.63 (m, 3H), 7.76 (s, 1H), 8.13-8.15 (m, 2H), 8.52 (d, J=6.8 Hz, 1H)
48	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.64 - 1.72 (m, 3H), 2.38 (s, 3H), 3.32-3.40 (m, 4H), 5.35 (s, 1H), 6.51 - 6.58 (m, 2H), 7.21 - 7.29 (m, 2H), 7.60 (s, 1H), 7.77 (s, 1H), 7.83 (d, J=7.4 Hz, 1H), 8.11 (d, J=7.8 Hz, 2H), 8.41 (d, J=7.7 Hz, 2H), 12.83 (s, 1H)
50	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.63 - 1.74 (m, 3H), 2.37 (s, 3H), 2.93 (s, 3H), 3.02 (s, 3H), 5.35 (s, 1H), 6.51 - 6.57 (m, 2H), 7.15 (s, 1H), 7.20 - 7.26 (m, 1H), 7.56 - 7.62 (m, 3H), 7.77 (s, 1H), 7.82 (d, J=7.7 Hz, 1H), 8.19 (d, J=7.5 Hz, 2H), 8.45 (s, 1H), 12.81 (s, 1H)
51	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.63 (d, J=6.60 Hz, 3H), 2.38 (s, 3H), 5.20 - 5.28 (m, 1H), 6.48 (d, J=8.56 Hz, 1H), 6.56 (t, J=7.40 Hz, 1H), 6.94 (s, 1H), 7.21 (t, J=7.53 Hz, 1H), 7.59 (d, J=1.96 Hz, 1H), 7.77 (d, J=1.10 Hz, 1H), 7.79 - 7.83 (m, 1H), 7.91 - 7.96 (m, 1H), 8.15 - 8.20 (m, 1H), 8.24 (t, J=7.82 Hz, 1H), 8.40 (br d, J=5.99 Hz, 1H), 12.76 (br s, 1 H)
52	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 - 1.72 (m, 5H), 1.88 (br s, 2H), 2.37 (br s, 3H), 5.33 (br s, 1H), 6.52 (br d, J=8.68 Hz, 1H), 6.57 (br s, 1H), 7.11 (br s, 1H), 7.19 - 7.26 (m, 1H), 7.52 (br d, J=7.95 Hz, 2H), 7.56 (br s, 1H), 7.76 (br s, 1H), 7.83 (br d, J=7.58 Hz, 1H), 8.16 (br d, J=7.46 Hz, 2H), 8.44 (br s, 1H), 12.79 (br s, 1H)
53	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 - 1.72 (m, 5H), 1.88 (br s, 2H), 2.37 (br s, 3H), 5.33 (br s, 1H), 6.52 (br d, J=8.68 Hz, 1H), 6.57 (br s, 1H), 7.11 (br s, 1H), 7.19 - 7.26 (m, 1H), 7.52 (br d, J=7.95 Hz, 2H), 7.56 (br s, 1H), 7.76 (br s, 1H), 7.83 (br d, J=7.58 Hz, 1H), 8.16 (br d, J=7.46 Hz, 2H), 8.44 (br s, 1H), 12.79 (br s, 1H)
55	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.65 (d, J=5.6 Hz, 3H), 1.98 (s, 4H), 2.29 (s, 3H), 4.02 (s, 4H), 5.23 (d, J=5.9 Hz, 1H), 6.29 (d, J=8.5 Hz, 1H), 6.47 - 6.52 (m, 1H), 6.55 (d, J=8.3 Hz, 2H), 6.65 (s, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.31 (s, 1H), 7.43 (s, 1H), 7.72 - 7.80 (m, 3H), 7.90 (d, J=7.8 Hz, 1H)
56	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.60 Hz, 3H), 2.30 (s, 3H), 5.27 - 5.35 (m, 1H), 6.44 - 6.52 (m, 2H), 7.15 (t, J=6.91 Hz, 1H), 7.26 (s, 1H), 7.51 (d, J=1.96

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	Hz, 1H), 7.69 (s, 1H), 7.74 (d, J=7.37 Hz, 1H), 8.06 - 8.12 (m, 2H), 8.22 (d, J=10.51 Hz, 1H), 8.34 (br d, J=5.99 Hz, 1H), 12.69 (br s, 1H)
57	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.63 (d, J=6.60 Hz, 3H), 2.37 (s, 3H), 5.21 - 5.29 (m, 1H), 6.48 (d, J=8.44 Hz, 1H), 6.56 (t, J=7.27 Hz, 1H), 6.82 (s, 1H), 7.19 - 7.25 (m, 1H), 7.32 - 7.38 (m, 1H), 7.55 - 7.62 (m, 2H), 7.76 (d, J=1.34 Hz, 1H), 7.79 - 7.83 (m, 1H), 8.10 - 8.17 (m, 1H), 8.40 (d, J=6.24 Hz, 1H), 12.75 (br s, 1H)
58	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.8 Hz, 3H), 2.08 (s, 3H), 2.36 (s, 3H), 5.01-5.15 (m, 1H), 6.45 (dd, J=7.2, 4.4 Hz, 1H), 7.12-7.12 (m, 1H), 7.51-7.52 (m, 2H), 7.59-7.60 (m, 3H), 7.78-7.81 (m, 3H), 8.17 (s, 1H)
59	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.60 (d, J=6.60 Hz, 3H), 2.37 (s, 3H), 5.17-5.38 (m, 1H), 6.47 - 6.57 (m, 2H), 6.93 (s, 1H), 7.12 - 7.20 (m, 1H), 7.56 (d, J=2.08 Hz, 1H), 7.77 - 7.87 (m, 3H), 7.94 (td, J=7.76, 1.22 Hz, 1H), 8.06 - 8.16 (m, 2H), 8.29 - 8.41 (m, 1H), 12.76 (br s, 1H)
60	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.67 - 1.73 (m, 3H) 2.37 (s, 3H) 3.87 (s, 3H) 5.28 - 5.39 (m, 1H) 6.50 - 6.59 (m, 2H) 7.13 - 7.16 (m, 1H) 7.17 - 7.27 (m, 2H) 7.49 - 7.54 (m, 1H) 7.54 - 7.58 (m, 1H) 7.62 - 7.66 (m, 1H) 7.70 - 7.78 (m, 2H) 7.80 - 7.85 (m, 1H) 8.41 - 8.47 (m, 1H) 12.68 - 12.96 (m, 1H)
61	¹ H NMR (400.13 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.7 Hz, 3H), 2.40 (s, 3H), 5.15-5.21 (m, 1H), 6.51-6.58 (m, 2H), 7.20-7.23 (m, 1H), 7.64-7.83 (m, 7H), 8.13-8.16 (m, 2H), 12.97-13.03 (m, 1H)
62	¹ H NMR (400.13 MHz, DMSO-d ₆) δ ppm 1.60-1.78 (m, 3H), 2.40 (s, 3H), 5.14-5.19 (m, 1H), 6.41-6.48 (m, 1H), 6.50-6.55 (m, 1H), 7.15-7.19 (m, 1H), 7.77-7.82 (m, 7H), 8.14-8.16 (m, 2H)
63	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.65 (d, J=6.7 Hz, 3H), 2.31 (s, 3H), 5.25 (q, J=6.6 Hz, 1H), 6.41 (d, J=8.4 Hz, 1H), 6.47 (t, J=7.5 Hz, 1H), 6.84 (s, 1H), 7.10 (t, J=7.8 Hz, 1H), 7.35 - 7.43 (m, 1H), 7.55 (d, J=2.0 Hz, 1H), 7.72 - 7.77 (m, 1H), 7.78 - 7.86 (m, 2H), 7.89 (ddd, J=11.3, 7.5, 2.2 Hz, 1H)
64	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.69 (d, J=6.60 Hz, 3H), 5.27 - 5.36 (m, 1H), 6.50 (d, J=8.31 Hz, 1H), 6.60 (t, J=7.40 Hz, 1H), 7.11 (s, 1H), 7.23 (t, J=7.19 Hz, 1H), 7.57 - 7.67 (m, 3H), 7.70 - 7.76 (m, 1H), 7.82 - 7.86 (m, 1H), 8.10 - 8.18 (m, 2H), 8.39 (br d, J=5.62 Hz, 1H), 12.81 (br s, 1H)
65	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.47 (d, J=6.8 Hz, 3H), 2.04 (s, 3H), 2.38 (s, 3H), 5.46-5.47 (m, 1H), 6.53 (t, J=8.8 Hz, 1H), 7.12-7.14 (m, 1H), 7.18 (s, 1H), 7.58-7.60 (m, 3H), 7.62 (d, J=2.0 Hz, 1H), 7.72-7.74 (m, 3H)
66	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.68 (d, J=6.72 Hz, 3H), 2.33 - 2.40 (m, 3H), 3.87 (s, 3H), 5.28 - 5.38 (m, 1H), 6.50 - 6.59 (m, 2H), 6.98 - 7.00 (m, 1H), 7.11 - 7.16 (m, 2H), 7.21 - 7.26 (m, 1H), 7.54 - 7.56 (m, 1H), 7.73 - 7.76 (m, 1H), 7.81 - 7.85 (m, 1H), 8.10 (d, J=9.05 Hz, 2H), 8.44 (d, J=6.60 Hz, 1H), 12.77 (br s, 1H)
67	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.64 (d, J=6.60 Hz, 3H), 2.37 (s, 3H), 3.95 (s, 3H), 5.20 - 5.28 (m, 1H), 6.47 (d, J=8.56 Hz, 1H), 6.56 (t, J=7.52 Hz, 1H), 6.93 (s, 1H), 7.13 - 7.30 (m, 3H), 7.52 - 7.62 (m, 2H), 7.73 - 7.77 (m, 1H), 7.82 (dd, J=8.07,

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	1.59 Hz, 1H), 7.92 (dd, J=7.76, 1.65 Hz, 1H), 8.39 (br d, J=6.60 Hz, 1H), 12.71 - 12.86 (m, 1H)
68	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.67 (d, J=6.60 Hz, 3H), 2.37 (s, 3H), 5.35 - 5.44 (m, 1H), 6.52 - 6.60 (m, 2H), 7.20 - 7.27 (m, 2H), 7.52 - 7.60 (m, 2H), 7.76 (s, 1H), 7.82 (d, J=7.58 Hz, 1H), 7.85 - 7.91 (m, 2H), 8.40 (br d, J=6.11 Hz, 1H), 12.75 (br s, 1H)
69	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.8 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.07-5.11 (m, 1H), 6.26 (d, J=8.4 Hz, 1H), 6.32 (dd, J=11.6, 8.0 Hz, 1H), 7.14-7.16 (m, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.58-7.60 (m, 3H), 7.78-7.81 (m, 3H), 8.08 (d, J=6.0 Hz, 1H)
70	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.7 Hz, 3H), 2.38 (s, 3H), 5.00 (m, 1H), 6.43 (d, J=8.4 Hz, 1H), 6.56 (t, J=7.5 Hz, 1H), 7.20 (t, J=7.7 Hz, 1H), 7.58-7.68 (m, 4H), 7.76-7.82 (m, 4H), 8.33 (bd, J=6.0 Hz, 1H), 12.80 (bs, 1H)
71	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.69 (d, J=6.6 Hz, 3H), 2.37 (s, 3H), 5.36 (br t, J=6.4 Hz, 1H), 6.51-6.59 (m, 2H), 7.15-7.20 (m, 2H), 7.23 (t, J=7.8 Hz, 1H), 7.57 (s, 1H), 7.77 (br s, 2H), 7.83 (br d, J=7.9 Hz, 2H), 8.29-8.35 (m, 2H), 8.44 (br d, J=6.0 Hz, 1H), 12.80 (br s, 1H)
72	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.58 - 1.66 (m, 3H) 2.06 - 2.16 (m, 3H) 5.10 - 5.19 (m, 1H) 6.42 - 6.50 (m, 1H) 6.52 - 6.62 (m, 1H) 7.14 - 7.27 (m, 1H) 7.48 - 7.56 (m, 1H) 7.59 - 7.72 (m, 4H) 7.82 - 7.87 (m, 3H) 8.33 - 8.39 (m, 1H) 12.77 - 12.94 (m, 1H)
73	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.6 Hz, 3H), 2.09 (s, 3H), 2.37 (s, 3H), 3.17 (s, 1H), 5.12 (br d, J=5.4 Hz, 1H), 6.46 (d, J=8.6 Hz, 1H), 6.55 (t, J=7.5 Hz, 1H), 7.15-7.23 (m, 1H), 7.54 (s, 1H), 7.74-7.83 (m, 3H), 8.00 (d, J=7.1 Hz, 2H), 8.01 (s, 1H), 8.36 (br d, J=5.3 Hz, 1H), 12.79 (br s, 1H)
74	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.4 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.27-5.33 (m, 1H), 7.57-7.60 (m, 4H), 7.79-7.80 (m, 3H), 7.81 (d, J=2.4 Hz, 1H), 8.30 (s, 1H), 8.48 (s, 1H)
75	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.8 Hz, 3H), 1.90 (s, 3H), 2.36 (s, 3H), 5.01-5.05 (m, 1H), 6.40 (d, J=8.8 Hz, 1H), 6.52 (t, J=7.2 Hz, 1H), 7.15-7.17 (m, 1H), 7.33-7.34 (m, 1H), 7.52-7.54 (m, 2H), 7.78-7.80 (m, 2H), 7.84-7.88 (m, 1H), 8.38 (s, 1H)
76	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.8 Hz, 3H), 2.09 (s, 3H), 2.38 (s, 3H), 5.05-5.08 (m, 1H), 6.34-6.41 (m, 2H), 6.66 (d, J=7.6 Hz, 1H), 7.06 (t, J=8.0 Hz, 1H), 7.56-7.61 (m, 4H), 7.78-7.81 (m, 3H)
77	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.58 (d, J=6.8 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.07-5.13 (m, 1H), 6.42 (d, J=9.2 Hz, 1H), 7.32 (q, J=7.2 Hz, 1H), 7.50 (d, J=2 Hz, 1H), 7.58-7.60 (m, 3H), 7.78-7.80 (m, 3H), 7.85-7.86 (m, 1H), 8.33-8.36 (m, 1H), 13.17 (s, 1H)
78	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.66 (d, J=6.7 Hz, 3H), 2.16 (s, 3H), 2.41 (s, 3H), 5.14 - 5.21 (m, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.55 (t, J=7.5 Hz, 1H), 7.18

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	(t, J=7.7 Hz, 1H), 7.44 - 7.57 (m, 1H), 7.61 (s, 2H), 7.74 (t, J=9.3 Hz, 1H), 7.87 (s, 1H), 7.91 (d, J=7.9 Hz, 1H)
79	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.56 (br d, J=6.60 Hz, 3H) 2.38 (s, 3H) 5.04 (br s, 1H) 6.43 (d, J=8.56 Hz, 1H) 6.55 (t, J=7.46 Hz, 1H) 7.20 (t, J=7.76 Hz, 1H) 7.55 - 7.58 (m, 1H) 7.58 - 7.63 (m, 3H) 7.78 - 7.83 (m, 2H) 7.87 - 7.94 (m, 2H) 8.34 (br d, J=4.77 Hz, 1H) 12.70 - 12.93 (m, 1H)
80	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 1.77 (d, J=6.6 Hz, 3H), 5.40 (q, J=6.7 Hz, 1H), 6.48 (d, J=8.5 Hz, 1H), 6.60 (t, J=7.5 Hz, 1H), 6.93 (t, J=56.0 Hz, 1H), 7.06 (s, 1H), 7.21 (t, J=7.8 Hz, 1H), 7.50 - 7.56 (m, 1H), 7.67 - 7.82 (m, 3H), 7.94 (d, J=7.9 Hz, 1H), 8.22 - 8.26 (m, 2H)
81	¹ H NMR (400.21 MHz, DMSO-d ₆) δ ppm 1.66 (d, J= 6.6 Hz, 3H), 5.27 (s, 1H), 6.92-6.96 (m, 2H), 7.12 (d, J= 8.8 Hz, 1H), 7.39 (td, J= 8.4, 2.3 Hz, 1H), 7.58-7.64 (m, 1H), 7.96 (d, J= 2.2 Hz, 1H), 8.17-8.23 (m, 2H), 9.34-9.39 (m, 1H)
82	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.76 (d, J= 6.7 Hz, 3H), 5.46 (quintet, J= 6.6 Hz, 1H), 7.17 (d, J= 8.9 Hz, 1H), 7.26 (s, 1H), 7.32 (d, J= 8.9 Hz, 1H), 7.61-7.68 (m, 3H), 7.99 (d, J= 1.8 Hz, 1H), 8.19 (d, J= 7.3 Hz, 2H), 8.24 (s, 1H), 8.42 (d, J= 6.3 Hz, 1H), 13.22-13.23 (m, 1H)
83	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 (br d, J=6.4 Hz, 3H), 2.09 (s, 3H), 5.14 (br d, J=5.2 Hz, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.57 (t, J=7.4 Hz, 1H), 7.04 - 7.31 (m, 2H), 7.45 - 7.59 (m, 1H), 7.66 (dd, J=7.8, 2.3 Hz, 1H), 7.74 - 7.85 (m, 3H), 7.97 - 8.04 (m, 2H), 8.35 (br s, 1H), 12.82 (br s, 1H)
85	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (br d, J=6.36 Hz, 3H) 2.40 (s, 3H) 5.16 (br s, 1H) 6.49 (br d, J=8.56 Hz, 1H) 6.57 (br t, J=7.46 Hz, 1H) 7.23 (br t, J=7.70 Hz, 1H) 7.49 - 7.62 (m, 4H) 7.66 (br d, J=7.58 Hz, 2H) 7.79 - 7.87 (m, 2H) 8.13 (s, 1H) 8.38 (br d, J=5.50 Hz, 1H) 9.01 (s, 1H) 12.82 (br s, 1H)
86	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.73 (d, J= 6.7 Hz, 3H), 5.42 (quintet, J= 6.4 Hz, 1H), 6.54 (d, J= 8.5 Hz, 1H), 6.58-6.61 (m, 1H), 7.20-7.24 (m, 1H), 7.25 (s, 1H), 7.60-7.67 (m, 3H), 7.84 (dd, J= 1.5, 7.9 Hz, 1H), 7.95 (d, J= 2.0 Hz, 1H), 8.18-8.22 (m, 3H), 8.46 (d, J= 6.1 Hz, 1H), 12.82-12.89 (m, 1H)
87	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.73 (d, J= 6.7 Hz, 3H), 5.42 (quintet, J= 6.4 Hz, 1H), 6.54 (d, J= 8.5 Hz, 1H), 6.58-6.61 (m, 1H), 7.20-7.24 (m, 1H), 7.25 (s, 1H), 7.60-7.67 (m, 3H), 7.84 (dd, J= 1.5, 7.9 Hz, 1H), 7.95 (d, J= 2.0 Hz, 1H), 8.18-8.22 (m, 3H), 8.46 (d, J= 6.1 Hz, 1H), 12.82-12.89 (m, 1H)
88	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.74 (d, J= 6.7 Hz, 3H), 5.48-5.54 (m, 1H), 7.17 (d, J= 9.1 Hz, 1H), 7.32-7.34 (m, 2H), 7.68-7.73 (m, 1H), 7.99 (d, J= 1.9 Hz, 1H), 8.08-8.10 (m, 1H), 8.23 (d, J= 1.3 Hz, 1H), 8.28-8.33 (m, 1H), 8.39 (d, J= 6.4 Hz, 1H), 13.20-13.23 (m, 1H)
89	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (br d, J=6.6 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 3.79 (s, 3H), 5.07 - 5.24 (m, 1H), 6.78 - 6.89 (m, 1H), 7.04 - 7.14 (m, 1H), 7.48 - 7.55 (m, 1H), 7.57 - 7.67 (m, 3H), 7.76 - 7.89 (m, 3H), 7.93 - 8.07 (m, 1H), 12.06 - 12.42 (m, 1H)

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90	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.68 (d, J= 6.6 Hz, 3H), 5.32 (dd, J= 1.7, 2.5 Hz, 1H), 6.47-6.59 (m, 2H), 6.97 (s, 1H), 7.18-7.21 (m, 1H), 7.38 (td, J= 8.4, 1.9 Hz, 1H), 7.59-7.64 (m, 1H), 7.82-7.84 (m, 1H), 7.97 (d, J= 1.8 Hz, 1H), 8.16-8.22 (m, 2H), 8.63-8.65 (m, 1H)
91	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.64 (d, J= 6.1 Hz, 3H), 2.12 (s, 3H), 5.18-5.23 (m, 1H), 6.74 (s, 1H), 7.17-7.23 (m, 2H), 7.63 (s, 3H), 7.85 (s, 2H), 7.92-7.97 (m, 1H), 8.26 (s, 1H), 8.97-9.01 (m, 1H)
92	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.4 Hz, 3H), 1.94 (s, 3H), 2.38 (s, 3H), 5.05 (m, 1H), 6.42 (d, J=8.31 Hz, 1H), 6.54 (m, 1H), 7.19 (m, 1H), 7.46 (m, 1H), 7.55 (d, J=2.2 Hz, 1H), 7.62 (m, 1H), 7.73 (m, 1H), 7.79 (m, 2H), 8.34 (d, J=6.4 Hz, 1H), 12.74 (br s, 1H)
93	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.47-1.58 (m, 3H), 1.84 (d, J=1.6 Hz, 3H), 2.26-2.35 (m, 3H), 5.02 (quin, J=6.5 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H), 7.23-7.32 (m, 1H), 7.32-7.43 (m, 2H), 7.47-7.53 (m, 1H), 7.56-7.66 (m, 1H), 7.67-7.81 (m, 3H), 8.54 (br d, J=6.6 Hz, 1H)
94	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54 (d, J=6.7 Hz, 3H), 1.91 (d, J=1.4 Hz, 3H), 2.37 (s, 3H), 4.96 - 5.05 (m, 1H), 6.21 (d, J=8.5 Hz, 1H), 6.34 (dd, J=11.4, 8.0 Hz, 1H), 7.14 (td, J=8.2, 6.3 Hz, 1H), 7.41 - 7.54 (m, 3H), 7.64 - 7.72 (m, 1H), 7.76 - 7.81 (m, 2H), 8.09 (d, J=6.2 Hz, 1H), 13.19 (br s, 1H)
95	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.7 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.02 - 5.16 (m, 1H), 6.27 (d, J=8.6 Hz, 1H), 6.35 (dd, J=11.4, 8.0 Hz, 1H), 7.16 (td, J=8.3, 6.3 Hz, 1H), 7.41 - 7.54 (m, 2H), 7.58 - 7.72 (m, 3H), 7.78 (d, J=1.2 Hz, 1H), 7.95 - 8.22 (m, 1H), 13.19 (br s, 1H)
96	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.65-1.67 (d, J= 6.8 Hz, 3H), 2.10 (s, 3H), 5.24-5.29 (m, 1H), 7.14-7.16 (m, 1H), 7.29-7.31 (m, 1H), 7.69-7.74 (m, 2H), 7.95-7.99 (m, 1H), 8.00 (d, J= 1.9 Hz, 1H), 8.27 (d, J= 1.3 Hz, 1H), 8.33-8.35 (m, 1H), 13.12-13.15 (m, 1H)
97	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.15 - 5.19 (m, 1H), 6.16 (d, J=7.6 Hz, 1H), 6.27 (dd, J=10.0, 8.4 Hz, 1H), 6.84 (s, 1H), 6.98-7.02 (m, 1H), 7.44 - 7.71 (m, 2H), 8.58 (d, J=2.0 Hz, 1H), 7.62 - 7.72 (m, 1H), 7.75 - 7.76 (m, 1H), 8.06 (td, J=7.6, 1.6 Hz, 1H), 8.32 (br s, 1H), 13.19 (br s, 1H)
98	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.64 (d, J= 6.8 Hz, 3H), 1.95 (d, J= 1.3 Hz, 3H), 5.14-5.19 (m, 1H), 7.09 (d, J= 8.9 Hz, 1H), 7.27 (d, J= 8.9 Hz, 1H), 7.45-7.51 (m, 2H), 7.69-7.74 (m, 1H), 7.81 (td, J= 7.5, 1.4 Hz, 1H), 8.02 (d, J= 1.9 Hz, 1H), 8.28-8.31 (m, 2H), 13.14-13.16 (m, 1H)
99	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.68-1.69 (m, 3H), 1.94 (s, 3H), 5.23-5.24 (m, 1H), 7.16-7.17 (m, 1H), 7.38-7.41 (m, 2H), 7.58-7.61 (m, 1H), 7.91-7.93 (m, 1H), 8.03-8.07 (m, 1H), 8.35-8.36 (m, 2H), 13.20-13.27 (m, 1H)
100	¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.66 (d, J= 6.7 Hz, 3H), 2.10 (s, 3H), 5.27-5.31 (m, 1H), 7.13-7.15 (m, 1H), 7.28-7.29 (m, 1H), 7.84 (t, J= 7.8 Hz, 1H), 8.00 (d, J= 2.0 Hz, 1H), 8.11 (d, J= 7.9 Hz, 1H), 8.17 (d, J= 7.9 Hz, 1H), 8.30-8.33 (m, 3H), 13.14-

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	13.15 (m, 1H)
101	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (br d, J=6.5 Hz, 3H), 2.37-2.42 (m, 6H), 5.05 (br s, 1H), 7.11 (br d, J=8.8 Hz, 1H), 7.24 (br d, J=8.7 Hz, 1H), 7.57-7.64 (m, 4H), 7.76 (br d, J=7.3 Hz, 2H), 7.82 (s, 1H), 8.36 (br s, 1H)
102	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.64 (d, J= 6.6 Hz, 3H), 2.13 (s, 3H), 5.18-5.23 (m, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.59 (t, J= 7.5 Hz, 1H), 7.21 (t, J= 7.4 Hz, 1H), 7.63-7.64 (m, 3H), 7.82-7.86 (m, 3H), 7.93 (d, J= 1.0 Hz, 1H), 8.26 (s, 1H), 8.38 (d, J= 6.1 Hz, 1H), 12.79-12.87 (m, 1H)
103	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54 (d, J=6.7 Hz, 3H), 1.91 (d, J=1.4 Hz, 3H), 2.37 (s, 3H), 4.96 - 5.05 (m, 1H), 6.21 (d, J=8.5 Hz, 1H), 6.34 (dd, J=11.4, 8.0 Hz, 1H), 7.14 (td, J=8.2, 6.3 Hz, 1H), 7.41 - 7.54 (m, 3H), 7.64 - 7.72 (m, 1H), 7.76 - 7.81 (m, 2H), 8.09 (d, J=6.2 Hz, 1H), 13.19 (br s, 1H)
104	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54 (d, J=6.7 Hz, 3H), 1.91 (d, J=1.4 Hz, 3H), 2.37 (s, 3H), 4.96 - 5.05 (m, 1H), 6.21 (d, J=8.5 Hz, 1H), 6.34 (dd, J=11.4, 8.0 Hz, 1H), 7.14 (td, J=8.2, 6.3 Hz, 1H), 7.41 - 7.54 (m, 3H), 7.64 - 7.72 (m, 1H), 7.76 - 7.81 (m, 2H), 8.09 (d, J=6.2 Hz, 1H), 13.19 (br s, 1H)
105	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.7 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.02 - 5.16 (m, 1H), 6.27 (d, J=8.6 Hz, 1H), 6.35 (dd, J=11.4, 8.0 Hz, 1H), 7.16 (td, J=8.3, 6.3 Hz, 1H), 7.41 - 7.54 (m, 2H), 7.58 - 7.72 (m, 3H), 7.78 (d, J=1.2 Hz, 1H), 7.95 - 8.22 (m, 1H), 13.19 (br s, 1H)
106	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.7 Hz, 3H), 2.07 (s, 3H), 2.37 (s, 3H), 5.02 - 5.16 (m, 1H), 6.27 (d, J=8.6 Hz, 1H), 6.35 (dd, J=11.4, 8.0 Hz, 1H), 7.16 (td, J=8.3, 6.3 Hz, 1H), 7.41 - 7.54 (m, 2H), 7.58 - 7.72 (m, 3H), 7.78 (d, J=1.2 Hz, 1H), 7.95 - 8.22 (m, 1H), 13.19 (br s, 1H)
107	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.15 - 5.19 (m, 1H), 6.16 (d, J=7.6 Hz, 1H), 6.27 (dd, J=10.0, 8.4 Hz, 1H), 6.84 (s, 1H), 6.98-7.02 (m, 1H), 7.44 - 7.71 (m, 2H), 8.58 (d, J=2.0 Hz, 1H), 7.62 - 7.72 (m, 1H), 7.75 - 7.76 (m, 1H), 8.06 (td, J=7.6, 1.6 Hz, 1H), 8.32 (br s, 1H), 13.19 (br s, 1H)
108	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 5.15 - 5.19 (m, 1H), 6.16 (d, J=7.6 Hz, 1H), 6.27 (dd, J=10.0, 8.4 Hz, 1H), 6.84 (s, 1H), 6.98-7.02 (m, 1H), 7.44 - 7.71 (m, 2H), 8.58 (d, J=2.0 Hz, 1H), 7.62 - 7.72 (m, 1H), 7.75 - 7.76 (m, 1H), 8.06 (td, J=7.6, 1.6 Hz, 1H), 8.32 (br s, 1H), 13.19 (br s, 1H)
109	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (br d, J=6.6 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 3.79 (s, 3H), 5.07 - 5.24 (m, 1H), 6.78 - 6.89 (m, 1H), 7.04 - 7.14 (m, 1H), 7.48 - 7.55 (m, 1H), 7.57 - 7.67 (m, 3H), 7.76 - 7.89 (m, 3H), 7.93 - 8.07 (m, 1H), 12.06 - 12.42 (m, 1H)
110	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (br d, J=6.6 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 3.79 (s, 3H), 5.07 - 5.24 (m, 1H), 6.78 - 6.89 (m, 1H), 7.04 - 7.14 (m, 1H), 7.48 - 7.55 (m, 1H), 7.57 - 7.67 (m, 3H), 7.76 - 7.89 (m, 3H), 7.93 - 8.07 (m, 1H), 12.06 - 12.42 (m, 1H)

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111	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.72 Hz, 3H) 2.32 (s, 3H) 5.22 (br t, J=6.54 Hz, 1H) 6.43 (d, J=8.31 Hz, 1H) 6.50 (t, J=7.58 Hz, 1H) 7.12 - 7.17 (m, 1H) 7.53 (d, J=2.20 Hz, 1H) 7.55 - 7.61 (m, 3H) 7.73 - 7.79 (m, 2H) 7.99 (dd, J=6.54, 2.87 Hz, 2H) 8.33 (br d, J=5.75 Hz, 1H) 12.57 - 12.85 (m, 1H)
112	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 0.87 - 1.10 (m, 1H) 1.60 (d, J=6.60 Hz, 3H) 2.37 (s, 3H) 4.19 (s, 2H) 4.87 (s, 1H) 5.14 - 5.24 (m, 1H) 5.36 (d, J=1.59 Hz, 1H) 6.48 (d, J=8.44 Hz, 1H) 6.50 - 6.61 (m, 1H) 7.16 - 7.27 (m, 1H) 7.46 - 7.59 (m, 4H) 7.76 - 7.85 (m, 2H) 7.87 - 7.95 (m, 2H) 8.36 (br s, 1H) 12.77 (br s, 1H)
113	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.60 (d, J=17 Hz, 3H), 2.06 (s, 3H), 2.38 (s, 3H), 5.16-5.19 (m, 1H), 7.08-7.11 (d, J=9.2 Hz, 1H), 7.29-7.31 (d, J=8.8 Hz, 1H), 7.55 (s, 1H), 7.64-7.68 (m, 2H), 7.79 (s, 1H), 7.90-8.30 (m, 1H), 8.31 (s, 1H)
114	¹ H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.59 (d, J=6.7 Hz, 3H), 2.00 (d, J=1.1 Hz, 3H), 2.34 (s, 3H), 5.01 (br d, J=3.8 Hz, 1H), 6.74 (d, J=9.0 Hz, 1H), 7.05-7.09 (m, 1H), 7.24-7.30 (m, 1H), 7.37 (d, J=2.1 Hz, 1H), 7.41-7.59 (m, 3H), 7.90 (s, 1H), 8.11 (br s, 1H)
115	¹ H NMR (400 MHz, CHLOROFORM-d) d ppm 1.59 (d, J=6.7 Hz, 3H), 2.00 (d, J=1.1 Hz, 3H), 2.34 (s, 3H), 5.01 (br d, J=3.8 Hz, 1H), 6.74 (d, J=9.0 Hz, 1H), 7.04-7.09 (m, 1H), 7.24-7.29 (m, 1H), 7.37 (d, J=2.1 Hz, 1H), 7.42-7.58 (m, 3H), 7.89-7.92 (m, 1H), 8.11 (br s, 1H)
116	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.53 (d, J = 6.63 Hz, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 4.97 (m, 1H), 6.87 (m, 1H), 7.00 - 7.09 (m, 1H), 7.55 - 7.70 (m, 5H), 7.73 - 7.83 (m, 3H), 8.62 - 8.89 (br s, 1H)
117	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.61 (d, J=6.6 Hz, 3H), 1.76 (s, 6H), 2.12 (s, 3H), 2.37 (s, 3H), 5.14 (br t, J=6.1 Hz, 1H), 6.44 (d, J=8.3 Hz, 1H), 6.55 (t, J=7.3 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.64-7.70 (m, 1H), 7.74-7.83 (m, 4H), 7.97 (s, 1H), 8.36 (br d, J=5.7 Hz, 1H), 12.74 (br s, 1H)
118	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.50 (s, 6H), 1.62 (d, J=6.6 Hz, 3H), 2.08-2.15 (m, 3H), 2.37 (s, 3H), 5.14 (br s, 1H), 6.42 (d, J=8.4 Hz, 1H), 6.55 (t, J=7.5 Hz, 1H), 6.99 (s, 1H), 7.05 (s, 1H), 7.21 (t, J=7.8 Hz, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.56 (d, J=5.0 Hz, 2H), 7.65-7.72 (m, 1H), 7.77-7.83 (m, 3H), 8.37 (br s, 1H), 12.61-12.98 (m, 1H)
119	¹ H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.72 (d, J=6.8 Hz, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 5.22 (q, J=6.6 Hz, 1H), 6.39 (d, J=8.5 Hz, 1H), 6.67 (t, J=7.5 Hz, 1H), 7.50-7.65 (m, 4H), 7.65-7.72 (m, 2H), 7.93-8.00 (m, 1H), 8.03 (dd, J=8.1, 1.4 Hz, 1H)
120	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.60 (d, J=6.8 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 5.12-5.19 (m, 1H), 7.11 (d, J=9.4 Hz, 1H), 7.32-7.33 (m, 1 H), 7.55 (s, 1H), 7.64-7.68 (m, 2H), 7.79-7.83 (m, 2H), 7.89-7.98 (m, 1H), 8.63-8.69 (m, 1H)
121	¹ H NMR (500 MHz, CDCl ₃) δ ppm 1.70 (d, J=6.5 Hz, 3H), 2.17 (s, 3H) 2.42 (s, 3H), 5.03-5.06 (m, 1H), 6.79 (d, J=9.0 Hz, 1H), 7.17 (d, J=9.0 Hz, 1H), 7.45 (s, 1 H), 7.71 (t, J=8.0 Hz, 1 H), 7.87 (dd, J=16.5, 7.5 Hz, 2H), 7.92 (s, 1H), 7.98 (s, 1H), 8.24 (s, 1H), 10.83 (br s, 1H)

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122	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.67 (d, J= 6.7 Hz, 3H), 2.13 (s, 3H), 5.21-5.27 (m, 1H), 7.13 (d, J= 8.5 Hz, 1H), 7.32 (dd, J= 4.4, 8.6 Hz, 1H), 7.62-7.64 (m, 3H), 7.85-7.87 (m, 3H), 7.97 (d, J= 2.1 Hz, 1H), 8.27 (d, J= 1.7 Hz, 1H), 8.64 (d, J= 6.7 Hz, 1H)
123	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.60 (d, J=6.4 Hz, 3H), 2.05 (s, 3H), 2.37 (s, 3H), 5.16-5.19 (m, 1H), 7.02 (d, J=8.8 Hz, 1H), 7.52 (d, J=9.2 Hz, 1H), 7.57 (d, J=2.0 Hz, 1H), 7.66-7.68 (m, 2H), 7.78 (s, 1H), 7.91-7.93 (m, 1H), 9.15 (br s, 1H)
124	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.8 Hz, 3 H), 2.06 (s, 3H), 2.34-2.37 (m, 6H), 5.14-5.17 (m, 1H), 7.07 (d, J=8.8 Hz, 1H), 7.20 (d, J=8.8 Hz, 1H), 7.53 (d, J=2.0 Hz, 1H), 7.64-7.69 (m, 2H), 7.78-7.79 (m, 1H), 7.91-7.95 (m, 1H), 8.42 (d, J=6.8 Hz, 1H)
125	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.54-1.60 (m, 3H), 2.04-2.07 (m, 3H), 2.29-2.36 (m, 3H), 5.08-5.18 (m, 1H), 6.93-7.21 (m, 2H), 7.24-7.31 (m, 1H), 7.37-7.48 (m, 1H), 7.50-7.58 (m, 1H), 7.75-7.82 (m, 2H), 8.03-8.07 (m, 1H), 8.11-8.16 (m, 1H), 8.31 (s, 1H)
126	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.63 (d, J=6.8 Hz, 3H), 2.05 (s, 3H), 2.38 (s, 3H), 5.23-5.27 (m, 1H), 7.14 (d, J=8.8 Hz, 1H), 7.60-7.66 (m, 2H), 7.79-7.81 (m, 2H), 8.05 (d, J=8.0 Hz, 1H), 8.12 (d, J=8.0 Hz, 1H), 8.29 (s, 1H), 8.60 (br s, 1H)
127	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.4 Hz, 3H), 2.06 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 5.15-5.19 (m, 1H), 7.04 (d, J=4.4 Hz, 1H), 7.16 (d, J=8.8 Hz, 1H), 7.54 (s, 1H), 7.78-7.83 (m, 2H), 8.06 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.0 Hz, 1H), 8.29 (s, 1H), 8.46 (s, 1H)
128	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.8 Hz, 3H), 2.06 (s, 3H), 2.39 (s, 3H), 5.20-5.29 (m, 1H), 6.68 (d, J=9.2 Hz, 1H), 7.48 (s, 1H), 7.57 (s, 1H), 7.78-7.82 (m, 2H), 8.02-8.07 (m, 1H), 8.12 (d, J=8.0 Hz, 1H), 8.29 (s, 1H), 8.73 (d, J=6.4 Hz, 1H)
129	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.57 (d, J=6.4 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 5.10-5.13 (m, 1H), 6.48 (dd, J=9.6, 4.8 Hz, 1H), 7.11-7.14 (m, 1H), 7.48-7.49 (m, 1H), 7.50-7.52 (m, 1H), 7.78-7.79 (m, 1H), 7.80-7.82 (m, 1H), 8.06 (d, J=7.6 Hz, 1H), 8.13 (d, J=8.0 Hz, 2H), 8.28 (s, 1H), 13.07 (br s, 1H)
130	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.72 Hz, 3H), 1.91 (d, J=1.34 Hz, 3H), 2.38 (s, 3H), 5.01 (br t, J=6.48 Hz, 1H), 6.23 (d, J=8.56 Hz, 1H), 6.34 (dd, J=11.43, 7.89 Hz, 1H), 7.15 (td, J=8.28, 6.30 Hz, 1H), 7.35 (td, J=8.38, 2.32 Hz, 1H), 7.52 - 7.58 (m, 2H), 7.78 - 7.90 (m, 2H), 8.07 (br d, J=6.36 Hz, 1H), 13.12 (br s, 1H)
131	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.72 Hz, 3H), 1.90 (d, J=1.34 Hz, 3H), 2.39 (s, 3H), 5.07 (quin, J=6.69 Hz, 1H), 7.04 (d, J=9.17 Hz, 1H), 7.19 - 7.39 (m, 2H), 7.49 - 7.61 (m, 2H), 7.79 - 7.89 (m, 2H), 8.27 (d, J=6.85 Hz, 1H), 12.48 - 13.32 (m, 1H)
132	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.72 Hz, 3H), 2.32 (s, 3H), 5.22 (br t, J=6.54 Hz, 1H), 6.43 (d, J=8.31 Hz, 1H), 6.50 (t, J=7.58 Hz, 1H), 7.12 - 7.17 (m, 1H), 7.53 (d, J=2.20 Hz, 1H), 7.55 - 7.61 (m, 3H), 7.73 - 7.79 (m, 2H), 7.99 (dd, J=6.54, 2.87 Hz, 2H), 8.33 (br d, J=5.75 Hz, 1H), 12.57 - 12.85 (m, 1H)

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133	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.72 Hz, 3H) 2.32 (s, 3H) 5.22 (br t, J=6.54 Hz, 1H) 6.43 (d, J=8.31 Hz, 1H) 6.50 (t, J=7.58 Hz, 1H) 7.12 - 7.17 (m, 1H) 7.53 (d, J=2.20 Hz, 1H) 7.55 - 7.61 (m, 3H) 7.73 - 7.79 (m, 2H) 7.99 (dd, J=6.54, 2.87 Hz, 2H) 8.33 (br d, J=5.75 Hz, 1H) 12.57 - 12.85 (m, 1H)
134	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.60 (d, J= 6.7 Hz, 3H), 2.08 (s, 3H), 2.37 (d, J= 2.4 Hz, 6H), 5.13-5.18 (m, 1H), 7.06 (d, J= 8.8 Hz, 1H), 7.20 (d, J= 8.8 Hz, 1H), 7.20 (d, J= 8.8 Hz, 1H), 7.45-7.48 (m, 1H), 7.53 (d, J= 2.0 Hz, 1H), 7.63-7.68 (m, 3H), 7.79 (d, J= 1.2 Hz, 1H), 8.41 (d, J= 6.8 Hz, 1H)
135	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.59 (d, J=6.7 Hz, 3H), 2.03 - 2.13 (m, 3H), 2.32 - 2.42 (m, 3H), 3.80 (s, 3H), 5.07 - 5.24 (m, 1H), 6.69 - 6.90 (m, 1H), 7.01 - 7.19 (m, 1H), 7.44 - 7.55 (m, 1H), 7.55 - 7.65 (m, 3H), 7.76 - 7.86 (m, 3H), 7.91 - 8.07 (m, 1H), 11.99 - 12.64 (m, 1H)
136	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.62 (d, J= 6.7 Hz, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 5.18 (quintet, J= 6.5 Hz, 1H), 7.13 (d, J= 8.3 Hz, 1H), 7.35 (dd, J= 4.5, 8.6 Hz, 1H), 7.43-7.47 (m, 1H), 7.56 (d, J= 1.8 Hz, 1H), 7.63-7.70 (m, 3H), 7.80 (d, J= 1.1 Hz, 1H), 7.84 (dd, J= 1.0, 4.4 Hz, 1H), 8.63 (d, J= 6.6 Hz, 1H)
137	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.59 (d, J= 6.8 Hz, 3H), 2.09 (s, 3H), 2.40 (s, 3H), 5.79-5.85 (m, 1H), 6.58-6.61 (m, 1H), 7.57-7.59 (m, 4H), 7.77-7.79 (m, 3H), 8.07-8.10 (m, 1H), 8.15 (dd, J= 1.8, 4.7 Hz, 1H), 8.56 (d, J= 7.3 Hz, 1H), 13.11-13.21 (m, 1H)
138	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.64 (d, J= 6.4 Hz, 3H), 2.08 (s, 3H), 2.39 (s, 3H), 5.30 (t, J= 6.0 Hz, 1H), 7.60 (d, J= 12.3 Hz, 4H), 7.80-7.84 (m, 4H), 7.92 (d, J= 5.2 Hz, 1H), 8.06 (s, 1H), 8.18 (d, J= 5.5 Hz, 1H)
139	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.50 (d, J= 6 Hz, 3H), 2.32 (s, 3H), 4.97 (m, 1H), 6.97 (d, J= 8 Hz, 1H), 7.18 (d, J= 8 Hz, 1H), 7.54 (m, 4H), 7.67 (m, 2H), 7.75 (m, 1H), 8.19 (d, J= 8 Hz, 1H), 13.0 (br s, 1H)
140	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.51 (d, J= 6.6 Hz, 3H), 2.31 (s, 3H), 4.99 (m, 1H), 6.98 (d, J= 12 Hz, 1H), 7.19 (d, J= 8.93 Hz, 1H), 7.52 (m, 4H), 7.74 (m, 1H), 7.81 (m, 2H), 8.22 (d, J= 8 Hz, 1H), 12.97 (br s, 1H)
141	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.8 Hz, 3H), 2.03 (s, 3H), 2.38 (s, 3H), 3.81 (s, 3H), 5.15-5.22 (m, 1H), 7.07 (d, J=8.8 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 7.60 (d, J=2.0 Hz, 1H), 7.78-7.82 (m, 2H), 8.07 (d, J=8.0 Hz, 1H), 8.11 (d, J=7.6 Hz, 2H), 8.29 (s, 1H)
142	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.60 (d, J= 6.7 Hz, 3H), 1.92 (d, J= 1.3 Hz, 3H), 2.38 (s, 3H), 5.09 (quintet, J= 6.7 Hz, 1H), 7.03 (d, J= 8.1 Hz, 1H), 7.31 (dd, J= 4.5, 8.6 Hz, 1H), 7.42-7.49 (m, 2H), 7.57 (d, J= 2.0 Hz, 1H), 7.67-7.71 (m, 1H), 7.78-7.83 (m, 3H), 8.60 (d, J= 6.8 Hz, 1H)
143	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.58 (d, J=6.63 Hz, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 5.10 (br t, J=6.19 Hz, 1H), 6.28 (d, J=8.63 Hz, 1H), 6.35 (dd, J=10.94, 8.57 Hz, 1H), 7.16 (q, J=7.63 Hz, 1H), 7.41 - 7.50 (m, 1H), 7.54 (s, 1H), 7.62 - 7.69 (m, 3H), 7.79 (s, 1H), 8.07 (br d, J=5.75 Hz, 1H), 13.17 (br s, 1H)

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144	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.54 (d, J=6.8 Hz, 3H), 2.07 (s, 3H), 2.36 (s, 3H), 5.05-5.07 (m, 1H), 7.32 (d, J=8.8 Hz, 1H), 7.00 (d, J=8.8 Hz, 1H), 7.50 (s, 1H), 7.77-7.83 (m, 3H), 8.07 (d, J=7.6 Hz, 1H), 8.16 (d, J=8.0 Hz, 1H), 8.31 (s, 1H), 9.47 (br s, 1H)
145	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.57 (d, J=6.4 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 5.09-5.11 (m, 1H), 6.44 (d, J=8.8 Hz, 1H), 7.15-7.17 (m, 1H), 7.40-7.47 (m, 1H), 7.51 (s, 1H), 7.64-7.68 (m, 3H), 7.74-7.76 (m, 1H), 7.77-7.78 (m, 1H), 8.69 (br s, 1H)
146	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.58 (d, J=6.8 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 5.10-5.13 (m, 1H), 6.51 (d, J=9.2 Hz, 1H), 7.23 (dd, J=8.8, 2.4 Hz, 1H), 7.51 (d, J=2.0 Hz, 1H), 7.61-7.69 (m, 2H), 7.72 (d, J=2.8 Hz, 1H), 7.78 (s, 1H), 7.90-7.94 (m, 1H), 8.33 (d, J=5.6 Hz, 1H), 13.18 (br s, 1H)
147	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.55 (d, J=6.8 Hz, 3H), 1.91 (s, 3H), 2.37 (s, 3H), 5.01-5.04 (m, 1H), 6.43 (d, J=9.2 Hz, 1H), 7.20 (dd, J=9.2, 2.8 Hz, 1H), 7.41-7.49 (m, 2H), 7.52 (d, J=2.0 Hz, 1H), 7.65-7.72 (m, 2H), 7.75-7.79 (m, 2H), 8.32 (d, J=6.0 Hz, 1H), 13.16 (br s, 1H)
148	¹ H NMR (500.11 MHz, DMSO-d6) d ppm 1.58 (d, J= 6.7 Hz, 3H), 1.91 (d, J= 1.1 Hz, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 5.07 (quintet, J= 6.7 Hz, 1H), 6.98 (d, J= 8.8 Hz, 1H), 7.17 (d, J= 8.7 Hz, 1H), 7.42-7.49 (m, 2H), 7.54 (d, J= 1.9 Hz, 1H), 7.66-7.71 (m, 1H), 7.77-7.80 (m, 2H), 8.38 (d, J= 6.9 Hz, 1H)
149	¹ H NMR (500.11 MHz, DMSO-d6) d ppm 1.59 (d, J= 6.3 Hz, 3H), 2.08 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 5.12 (t, J= 5.9 Hz, 1H), 6.48 (d, J= 8.3 Hz, 1H), 6.55 (t, J= 7.3 Hz, 1H), 7.21 (t, J= 7.5 Hz, 1H), 7.56 (s, 1H), 7.79-7.82 (m, 2H), 7.95 (d, J= 7.9 Hz, 2H), 8.14 (d, J= 8.0 Hz, 2H), 8.35 (d, J= 5.4 Hz, 1H), 12.68-12.83 (m, 1H)
150	¹ H NMR (500.11 MHz, DMSO-d6) d ppm 1.60 (d, J= 6.7 Hz, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 3.89 (s, 3H), 5.12 (quintet, J= 6.3 Hz, 1H), 6.47 (d, J= 8.5 Hz, 1H), 6.55 (t, J= 7.5 Hz, 1H), 7.19-7.23 (m, 1H), 7.54 (d, J= 1.8 Hz, 1H), 7.75-7.81 (m, 3H), 8.10 (d, J= 8.0 Hz, 1H), 8.16 (d, J= 7.9 Hz, 1H), 8.35-8.37 (m, 2H), 12.81-12.83 (m, 1H)
151	¹ H NMR (500.11 MHz, DMSO-d6) d ppm 1.60 (d, J= 6.7 Hz, 3H), 2.10 (s, 3H), 2.37 (s, 3H), 2.84 (d, J= 4.5 Hz, 3H), 5.13 (quintet, J= 6.4 Hz, 1H), 6.47 (d, J= 8.5 Hz, 1H), 6.55 (t, J= 7.5 Hz, 1H), 7.20-7.23 (m, 1H), 7.54 (d, J= 1.8 Hz, 1H), 7.79-7.82 (m, 2H), 7.90 (d, J= 8.3 Hz, 2H), 8.01 (d, J= 8.3 Hz, 2H), 8.36 (d, J= 6.3 Hz, 1H), 8.62 (q, J= 4.2 Hz, 1H), 12.76 (s, 1H)
152	¹ H NMR (500.11 MHz, DMSO-d6) d ppm 1.59 (d, J= 6.7 Hz, 3H), 2.09 (s, 3H), 2.38 (s, 3H), 2.83 (d, J= 4.4 Hz, 3H), 5.12-5.16 (m, 1H), 6.45-6.47 (m, 1H), 6.55 (t, J= 7.5 Hz, 1H), 7.19-7.22 (m, 1H), 7.54 (d, J= 1.8 Hz, 1H), 7.70 (t, J= 7.7 Hz, 1H), 7.80-7.82 (m, 2H), 7.96 (d, J= 7.7 Hz, 1H), 8.04 (d, J= 7.9 Hz, 1H), 8.23 (s, 1H), 8.36 (d, J= 6.0 Hz, 1H), 8.60 (d, J= 4.3 Hz, 1H), 12.70-12.79 (m, 1H)
155	¹ H NMR (400 MHz, DMSO-d6) δ ppm 1.53 (d, J=6.6 Hz, 3H), 1.96 - 2.03 (m, 3H), 2.28 - 2.33 (m, 3H), 3.73 (s, 3H), 5.06 - 5.29 (m, 1H), 7.19 - 7.44 (m, 1H), 7.44 - 7.64 (m, 4H), 7.65 - 7.90 (m, 3H), 7.96 - 8.25 (m, 1H), 13.02 - 13.71 (m, 1H)

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156	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.65 (d, J=6.6 Hz, 3H), 2.41 (s, 3H), 5.21 (br s, 1H), 6.49-6.55 (m, 1H), 6.58 (t, J=7.5 Hz, 1H), 7.17-7.31 (m, 1H), 7.38-7.44 (m, 2H), 7.44-7.53 (m, 3H), 7.64 (d, J=2.0 Hz, 1H), 7.67-7.75 (m, 1H), 7.82-7.86 (m, 2H), 7.97 (br d, J=7.8 Hz, 1H), 8.39 (br s, 1H), 8.70 (br s, 1H), 12.79 (br s, 1H)
157	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.6 Hz, 3H), 1.97 - 2.04 (m, 3H), 2.28 - 2.34 (m, 3H), 5.15 (quin, J=6.4 Hz, 1H), 6.40 - 6.72 (m, 1H), 7.39 - 7.61 (m, 5H), 7.61 - 7.89 (m, 3H), 7.90 - 8.20 (m, 1H), 8.67 - 8.95 (m, 1H), 13.18 - 13.47 (m, 1H)
158	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.55 (d, J=6.6 Hz, 3H), 1.97 - 2.04 (m, 3H), 2.28 - 2.34 (m, 3H), 5.15 (quin, J=6.4 Hz, 1H), 6.40 - 6.72 (m, 1H), 7.39 - 7.61 (m, 5H), 7.61 - 7.89 (m, 3H), 7.90 - 8.20 (m, 1H), 8.67 - 8.95 (m, 1H), 13.18 - 13.47 (m, 1H)
159	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.64 (d, J=6.7 Hz, 3H), 2.08 (s, 3H), 2.39 (s, 3H), 5.14 - 5.30 (m, 1H), 7.09 (d, J=9.2 Hz, 1H), 7.53 - 7.66 (m, 4H), 7.68 - 7.90 (m, 4H), 8.69 - 8.87 (m, 1H), 13.33 - 13.63 (m, 1H)
160	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.64 (d, J=6.7 Hz, 3H), 2.08 (s, 3H), 2.39 (s, 3H), 5.14 - 5.30 (m, 1H), 7.09 (d, J=9.2 Hz, 1H), 7.53 - 7.66 (m, 4H), 7.68 - 7.90 (m, 4H), 8.69 - 8.87 (m, 1H), 13.33 - 13.63 (m, 1H)
161	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.6 Hz, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 5.19-5.14 (m, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.56 (t, J= 7.5 Hz, 1H), 7.24-7.21 (m, 1H), 7.54 (d, J= 1.8 Hz, 1H), 7.68 (d, J= 8.3 Hz, 2H), 7.84-7.79 (m, 4H), 7.97-7.91 (m, 1H), 8.37 (d, J= 5.7 Hz, 1H), 12.94-12.93 (m, 2H)
162	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.7 Hz, 3H), 2.14 (s, 3H), 2.37 (s, 3H), 5.14-5.19 (m, 1H), 6.46-6.49 (m, 1H), 6.54-6.57 (m, 1H), 7.20-7.24 (m, 1H), 7.53 (d, J= 1.9 Hz, 1H), 7.78-7.85 (m, 6H), 8.41-8.43 (m, 3H), 13.16-13.20 (m, 2H)
163	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.70 (d, J= 6.7 Hz, 3H), 2.37 (s, 3H), 5.33-5.37 (m, 1H), 6.53-6.57 (m, 2H), 7.10 (s, 1H), 7.26-7.28 (m, 1H), 7.54-7.56 (m, 1H), 7.76 (d, J= 1.3 Hz, 1H), 7.84 (d, J= 8.6 Hz, 3H), 8.13 (d, J= 8.6 Hz, 2H), 8.17-8.63 (br, 3H), 13.16-13.18 (br, 2H)
164	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.7 Hz, 3H), 2.14 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 5.13-5.18 (m, 1H), 6.47 (d, J= 8.5 Hz, 1H), 6.56 (t, J= 7.5 Hz, 1H), 7.20-7.24 (m, 1H), 7.53 (d, J= 1.9 Hz, 1H), 7.77-7.83 (m, 6H), 8.00 (s, 1H), 8.28 (s, 1H), 8.35-8.41 (m, 1H), 13.05-13.11 (m, 1H)
165	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.62 (d, J= 6.7 Hz, 3H), 2.16 (s, 3H), 2.29 (s, 6H), 2.38 (s, 3H), 5.16-5.21 (m, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.56 (t, J= 7.6 Hz, 1H), 7.21-7.24 (m, 1H), 7.51-7.54 (m, 3H), 7.79-7.86 (m, 4H), 8.33-8.36 (m, 1H)
166	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.7 Hz, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 5.14-5.18 (m, 1H), 6.45-6.48 (m, 1H), 6.52-6.56 (m, 1H), 6.82 (d, J= 2.3 Hz, 1H), 7.19-7.22 (m, 1H), 7.51-7.53 (m, 1H), 7.62-7.67 (m, 1H), 7.71-7.75 (m, 1H), 7.76-7.82 (m, 4H), 8.01-8.04 (m, 1H), 8.23 (s, 1H), 8.40-8.41 (m, 1H), 13.09-13.12 (m, 1H)

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167	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.60 (d, J= 6.7 Hz, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 5.12-5.17 (m, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.55 (t, J= 7.6 Hz, 1H), 7.20-7.23 (m, 1H), 7.54 (d, J= 1.9 Hz, 1H), 7.56-7.62 (m, 2H), 7.80-7.84 (m, 3H), 8.03 (s, 1H), 8.22-8.24 (m, 2H), 8.34-8.41 (m, 1H), 13.08-13.10 (m, 2H)
168	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.62 (d, J= 6.7 Hz, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 5.14-5.19 (m, 1H), 6.47-6.50 (m, 1H), 6.54-6.57 (m, 1H), 6.86 (d, J= 2.3 Hz, 1H), 7.21-7.24 (m, 1H), 7.54 (d, J= 2.0 Hz, 1H), 7.80-7.87 (m, 5H), 8.00-8.03 (m, 2H), 8.35-8.40 (m, 1H), 13.16-13.18 (m, 2H)
169	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.59-1.62 (m, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 3.96 (s, 3H), 5.15-5.19 (m, 1H), 6.46-6.51 (m, 1H), 6.54-6.57 (m, 2H), 7.21-7.24 (m, 1H), 7.51-7.57 (m, 2H), 7.77-7.83 (m, 4H), 7.94 (d, J= 8.2 Hz, 2H), 8.41-8.34 (m, 1H), 12.96-12.91 (m, 1H)
170	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.57 (d, J= 6.7 Hz, 3H), 1.92 (d, J= 1.1 Hz, 3H), 2.39 (s, 3H), 5.04-5.09 (m, 1H), 6.43-6.45 (m, 1H), 6.53 (t, J= 7.5 Hz, 1H), 7.17-7.20 (m, 1H), 7.57 (d, J= 2.0 Hz, 1H), 7.65 (t, J= 7.8 Hz, 1H), 7.78 (dd, J= 1.6, 7.9 Hz, 1H), 7.80 (d, J= 1.2 Hz, 1H), 8.15-8.18 (m, 1H), 8.19-8.22 (m, 1H), 8.32-8.34 (m, 1H), 12.77-12.80 (m, 1H)
171	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 1.62 (d, J=6.6 Hz, 3H), 2.31-2.38 (m, 5H), 2.84-2.89 (m, 2H), 5.22 (br t, J=6.1 Hz, 1H), 6.48 (d, J=8.4 Hz, 1H), 6.56 (t, J=7.6 Hz, 1H), 7.19-7.24 (m, 1H), 7.49-7.53 (m, 2H), 7.56-7.60 (m, 2H), 7.79-7.83 (m, 2H), 8.04 (d, J=7.2 Hz, 2H), 8.37 (br d, J=6.1 Hz, 1H), 11.83 (s, 1H), 12.48-13.10 (m, 1H)
172	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.7 Hz, 3H), 2.14 (s, 3H), 2.38 (s, 3H), 5.13-5.18 (m, 1H), 6.49 (d, J= 8.5 Hz, 1H), 6.56 (t, J= 7.4 Hz, 1H), 7.21-7.24 (m, 1H), 7.55 (d, J= 1.7 Hz, 1H), 7.80-7.83 (m, 2H), 7.94-8.02 (m, 8H), 8.37 (d, J= 6.2 Hz, 1H), 12.73-12.76 (m, 1H)
173	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.6 Hz, 3H), 2.14 (s, 3H), 2.38 (s, 3H), 5.15 (t, J= 6.1 Hz, 1H), 6.49 (d, J= 8.5 Hz, 1H), 6.56 (t, J= 7.5 Hz, 1H), 7.23 (t, J= 7.6 Hz, 1H), 7.55 (s, 1H), 7.73 (t, J= 7.8 Hz, 1H), 7.79-7.83 (m, 2H), 7.89-7.99 (m, 5H), 8.14 (d, J= 7.9 Hz, 1H), 8.28 (s, 1H), 8.38 (d, J= 5.5 Hz, 1H), 12.77-12.83 (m, 1H)
174	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.59 (d, J= 6.6 Hz, 3H), 2.16 (s, 3H), 2.37 (s, 3H), 5.21-5.26 (m, 1H), 6.45 (d, J= 8.5 Hz, 1H), 6.53 (t, J= 7.5 Hz, 1H), 7.16-7.19 (m, 1H), 7.53 (d, J= 1.8 Hz, 1H), 7.61-7.65 (m, 1H), 7.73 (d, J= 7.6 Hz, 1H), 7.80-7.85 (m, 5H), 7.95 (d, J= 7.2 Hz, 1H), 8.00-8.03 (m, 2H), 8.35 (d, J= 6.1 Hz, 1H), 12.80-12.81 (m, 1H)
175	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.6 Hz, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 5.15 (quintet, J= 6.3 Hz, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.54 (t, J= 7.5 Hz, 1H), 7.18-7.21 (m, 1H), 7.55 (d, J= 1.5 Hz, 1H), 7.74 (t, J= 7.7 Hz, 1H), 7.80-7.81 (m, 2H), 7.89 (d, J= 7.7 Hz, 1H), 7.96-7.98 (m, 5H), 8.17 (s, 1H), 8.36 (d, J= 6.2 Hz, 1H), 12.66-12.79 (m, 1H)

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176	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.61 (d, J= 6.7 Hz, 3H), 2.14 (s, 3H), 2.38 (s, 3H), 5.16 (t, J= 6.1 Hz, 1H), 6.48 (d, J= 8.5 Hz, 1H), 6.53 (t, J= 7.5 Hz, 1H), 7.19-7.22 (m, 1H), 7.55 (d, J= 1.7 Hz, 1H), 7.69-7.75 (m, 2H), 7.79-7.81 (m, 2H), 7.87 (t, J= 6.7 Hz, 2H), 7.98 (d, J= 7.9 Hz, 1H), 8.11 (d, J= 8.0 Hz, 1H), 8.18 (s, 1H), 8.27 (s, 1H), 8.37 (d, J= 5.7 Hz, 1H), 12.83-12.84 (m, 1H)
177	¹ H NMR (500.11 MHz, DMSO-d ₆) δ ppm 1.62 (d, J= 6.7 Hz, 3H), 2.16 (s, 3H), 2.38 (s, 3H), 5.18 (quintet, J= 6.2 Hz, 1H), 6.49 (d, J= 8.6 Hz, 1H), 6.55 (t, J= 7.5 Hz, 1H), 7.21-7.24 (m, 1H), 7.55 (d, J= 2.0 Hz, 1H), 7.66 (td, J= 7.6, 1.0 Hz, 1H), 7.76 (d, J= 7.4 Hz, 1H), 7.83-7.88 (m, 5H), 7.99-8.03 (m, 3H), 8.36-8.43 (m, 1H), 12.87-12.89 (m, 1H)

[772] PI3K-Alpha kinase (PIK3CA) activity, wild-type and H1047R mutant and determining IC₅₀ values for inhibitors

[773] Recombinant, catalytically active human full length PIK3KA Wild-type and H1047R mutant were purchased as 1:1 complex of N-terminal 6X his tagged p110α (catalytic) and untagged p85α (regulatory subunit) from EMD Millipore Sigma (cat.no. 14-602M and 14-792M, respectively). PIP2diC8 (Avanti Polar Lipids Inc., cat.no.850185) or Soy PI (Avanti Polar Lipids Inc., cat. No. 840044P) was used as lipid substrate. PIP2diC8 or PI lyophilized powder was dissolved in milliQ water to a concentration of 1mM just before use. 10mM stock compounds in DMSO were serially diluted 1:3 to generate a 10-point curve and plated using an acoustic liquid handler system (Echo 550 series instrument, Labcyte). A 10X intermediate compound plate (200uM starting compound concentration and 10% DMSO) was prepared before starting the reaction. A typical reaction mixture (50 uL) comprised 40mM HEPES buffer, pH 7.4, 25 mM MgCl₂, 0.01% v/v triton-X-100, 1% v/v DMSO, 20 mM NaCl, 1-5 nM WT or H1047R PI3K protein, 20 uM ATP, and 50 uM PIP2diC8 or Soy PI. 1% DMSO buffer alone without test compound was employed as MAX control (full activity in the absence of any inhibitor), and no enzyme control was used to determine the level of background Adenosine 5'-diphosphate (ADP) (MIN control). First, Wild-type (WT) and H1047R mutant protein in kinase buffer with all components except ATP were incubated with or without compound at 27°C for 1h. After the pre-incubation, the reaction was initiated by the addition of 20uL of 50uM ATP (20uM final concentration). The reaction was allowed to proceed until about 10% conversion of ATP (2 uM ADP) at 27°C. After that time, 5 uL of reaction was mixed with 5 uL

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of ADP-Kinase Glo Reagent (ADP-Glo Kinase assay kit, Promega cat.no. V9102) supplemented with MgCl_2 10mM to stop the reaction and deplete the remaining ATP for 40 min at room temperature. Then, 10 μL of Kinase Detection Reagent (ADP-Glo Kinase assay kit, Promega cat.no. V9102) was added to simultaneously convert ADP to ATP and allow the newly synthesized ATP to be measured using a luciferase/luciferin reaction. After 30 min at room temperature the light generated was measured using a luminometer (EnVision plate reader, Perkin Elmer). Process data through Genedata-Screener tool. Relative IC_{50} values are determined using luminescence units by calculating percent inhibition with respect to on-plate “MIN” and “MAX” controls. Data was analyzed using a 4-parameter nonlinear logistic equation (four-parameter logistic concentration-response curve):

$$Y = \text{bot} + [(\text{top}-\text{bot})/1+(x/\text{IC}_{50})^{\text{slope}}]$$

where Y = % inhibition, X = concentration yielding y% inhibition, Bottom = minimum value of y attained by curve, Top = maximum value of y attained by curve and Slope = steepness of curve at IC_{50} .

$$\% \text{Inh} = [(\text{median Max} - x / \text{median Max} - \text{median Min})] \cdot 100$$

IC_{50} : concentration of compound that reduces a given response (ligand binding, enzyme response) by 50%. IC_{50} relative: concentration giving half the compound's maximum response.

[774] For IC_{50} values shown in Table A, “A” means $\text{IC}_{50} < 0.5 \mu\text{M}$; “B” means IC_{50} ranging between $0.5 \mu\text{M}$ and $1.0 \mu\text{M}$; “C” means IC_{50} ranging between $1 \mu\text{M}$ and $5 \mu\text{M}$; “D” means IC_{50} ranging between $5 \mu\text{M}$ and $10 \mu\text{M}$; “E” means $\text{IC}_{50} > 10 \mu\text{M}$.

Table A: PI3K- α (PIK3CA) Biochemical IC_{50} of PI3K wild-type (WT) and H1047R mutant, using Soy PI lipid substrate

Example #	IC_{50} H1047R	IC_{50} WT
1	A	B

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2	A	A
3	A	D
4	E	E
5	A	E
6 ¹	A	C
7 ¹	A	B
8	A	E
9	A	E
10	A	C
11	A	C
12	B	D
13	A	C
14	A	E
15	A	D
16 ¹	A	B
17 ¹	A	A
18 ¹	A	A
19 ¹	A	C
20 ¹	A	A
21	A	C
22 ¹	A	A
23	A	D
24	A	C
25	A	C
26	A	B
27	A	C

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28	A	C
29	A	B
30	A	B
31	A	C
32	A	D
33	A	D
34	A	E
35	A	C
36	B	D
37	B	C
38	A	A
39	A	C
40	A	D
41	A	C
42	A	B
43	A	C
44	A	C
45	A	E
46	A	D
47	E	E
48	A	E
49	A	D
50	D	E
51	A	C
52	D	D
53	A	C

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54	B	E
55	A	C
56	A	C
57	A	C
58	A	A
59	A	D
60	A	B
61	E	E
62	A	A
63	A	C
64	A	E
65	E	E
66	A	C
67	A	E
68	A	C
69	A	B
70	A	C
71	A	C
72	C	C
73	A	E
74	A	E
75	A	C
76	A	D
77	A	C
78	A	C
79	A	B

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80	A	D
81	A	C
82	A	C
83	A	D
84	A	D
85	A	C
86	E	D
87	A	D
88	A	C
89	A	C
90	A	D
91	A	C
92	A	D
93	C	E
94	A	C
95	A	C
96	A	C
97	A	C
98	A	C
99	A	B
100	A	B
101	A	A
102	A	C
103	A	A
104	B	E
105	A	C

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106	C	C
107	A	C
108	D	E
109	A	B
110	C	C
111	A	C
112	A	C
113	A	C
114	A	C
115	A	A
117	A	C
118	A	C
119	A	B
120	C	E
121	A	B
122	C	E
123	A	C
124	A	C
125	B	D
126	A	C
127	A	C
128	A	C
129	A	A
130	A	C
131	A	C
132	A	C

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133	A	C
134	A	D
135	A	B
136	B	D
137	A	C
138	A	E
139	A	A
140	A	C
141	A	A
142	C	E
144	A	B
145	A	C
146	C	C
147	B	C
148	B	D
149	A	C
150	A	C
151	A	C
152	A	E
153	C	C
154	A	B
155	A	C
156	B	C
157	D	D
158	A	C
159	A	B

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160	A	C
161	A	B
162	A	B
163	B	C
164	A	A
165	A	C
166	B	C
167	A	B
168	A	B
169	A	A
171	B	E

¹ PIP2diC8 lipid substrate*For Example 13, IC₅₀ WT/IC₅₀ H1047R = 7.7

[775] PI3K-Alpha kinase (PIK3CA) activity in vitro cell based assay and determining IC₅₀ values for inhibitors

[776] The MDA-MB-453 (ATCC-HTB-131) cell line was obtained from the American Type Culture Collection (Manassas, VA). Cells were maintained in Dulbecco's Modified Eagle Media (DMEM, Gibco 11965-092) supplemented with 10% Fetal Bovine Serum, heat inactivated (FBS HI, Gibco 10082-147), 1X non-essential amino acids (NEAA, Gibco 11140-050), and 1 mM sodium pyruvate (Gibco 11360-070). Cultures were maintained in a humidified incubator at 37°C under 5% CO₂/95% air.

For compound testing in 0% FBS, MDA-MB-453 cells were seeded at a density of 1.5×10⁴ cells per well in white 384-well plates in 20 µl of Minimum Essential Media (MEM) assay media with 1X NEAA, 1 mM sodium pyruvate, and 1 µg/mL human insulin (Sigma I9278). Compounds dissolved in 10 mM stock solutions in DMSO were serially diluted 1:3 in DMSO to generate a 10-point dilution series and plated using an acoustic liquid handler system (Echo 550 Series Liquid Handler,

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Labcyte). A 5X intermediate compound dilution plate in MEM with 1X NEAA and 1 mM sodium pyruvate (150 μ M starting compound concentration in 1.5% DMSO) was then prepared. Five μ L of the intermediate serially diluted compounds were added to the cell plate to final concentrations ranging from 30 mM to 0.0015 mM in 0.3% DMSO. 0.3% DMSO alone was used to establish the maximum (MAX) signal and GDC-0032 at a final concentration of 1 μ M was used as a reference compound for the minimum (MIN) signal. After 3 hours treatment, the medium was removed, and the cells lysed in 10 μ L of 1X SureFire Lysis buffer with shaking for 10 minutes at room temperature. The Acceptor Mix (Reaction Buffer 1 + Reaction Buffer 2 + Activation Buffer + SureFire Ultra Acceptor Beads) was prepared by diluting Activation buffer 25-fold in combined Reaction Buffer 1 and Reaction Buffer 2. The Acceptor beads were diluted 50-fold in the combined Reaction Buffers. Five μ L of Acceptor Mix was added to each well, the plate was sealed and covered with foil and incubated for 1 hour at room temperature. The Donor Mix (dilution buffer + SureFire Ultra Donor Beads) was prepared by diluting Donor Beads 50-fold in dilution buffer. Five μ L of the Donor Mix was added to each well and the plate sealed and covered with foil and incubated for 1 hour at room temperature in the dark. The plates were read on a Neo2 plate reader instrument from Biotek using standard AlphaLisa settings.

Compounds were tested in duplicate and the average % inhibition at each compound concentration was used to generate a single dose response curve. The data were processed using the Genedata-Screener tool. Relative IC₅₀ values were determined using luminescence units by calculating percent inhibition with respect to the in-plate "MIN" (GDC-0032 reference control) and "MAX" (DMSO) controls. The data was analyzed using a 4-parameter nonlinear logistic equation (four-parameter logistic concentration-response curve):

$$Y = \text{bottom} + [(\text{top} - \text{bottom}) / (1 + (X / \text{IC}_{50})^{\text{slope}})]$$

where Y = % inhibition, X = concentration of inhibitor, bottom = minimum value of y attained by curve-fit, top = maximum value of y attained by curve-fit and slope = steepness of curve at the IC₅₀.

$$\% \text{Inhibition} = [(\text{signal at X} - \text{median Min}) / (\text{median Max} - \text{median Min})] \times 100$$

IC₅₀: concentration of compound that reduces a given response (ligand binding, enzyme response) by 50%. Relative IC₅₀: concentration giving half the compound's maximum response.

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[777] For IC₅₀ values shown in Table B, “A” means IC₅₀ < 50 nM; “B” means IC₅₀ ranging between 50 nM and 100 nM; “C” means IC₅₀ ranging between 100 nM and 500 nM; “D” means IC₅₀ > 500 nM.

Table B: PI3K- α (PIK3CA) in vitro cell based assay IC₅₀

Example #	IC ₅₀
1	A
4	D
14	A
15	A
21	A
25	B
26	B
28	A
29	A
30	A
31	A
32	A
33	C
35	A
36	B
37	C
38	A
39	A
40	B
41	A

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42	A
43	B
44	A
50	D
52	D
55	C
58	A
60	A
62	A
63	A
66	A
67	B
68	A
69	A
70	A
73	A
75	A
76	A
78	A
81	A
84	D
85	A
88	A
91	A
92	A
93	C

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94	A
95	A
96	A
98	A
99	A
101	A
102	A
104	C
105	A
106	D
108	D
109	A
110	D
111	A
112	B
113	A
114	A
115	A
116	A
117	A
118	C
119	A
120	B
121	A
122	B
123	A

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124	A
125	B
126	A
127	B
128	B
129	A
130	A
131	A
132	A
133	B
134	A
135	A
136	B
137	A
138	C
140	A
141	A
142	B
143	A
144	A
145	A
146	A
147	A
148	A
149	A
150	A

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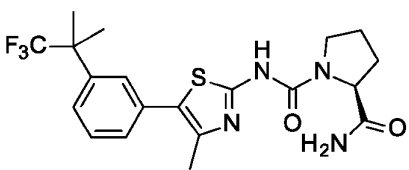
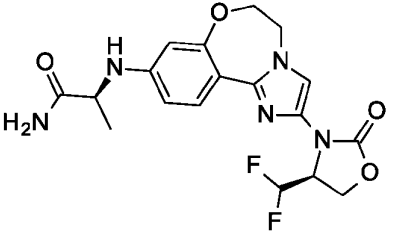
151	A
152	A
155	C
156	C
157	D
158	A
159	A
160	C
161	A
162	A
163	B
164	A
165	A
166	A
167	A
168	A
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173	B
174	A
175	B
176	B
177	A
178	A

- 400 -

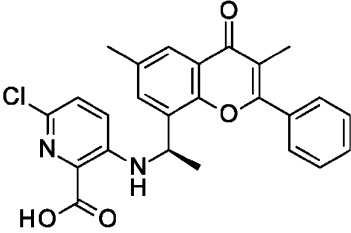
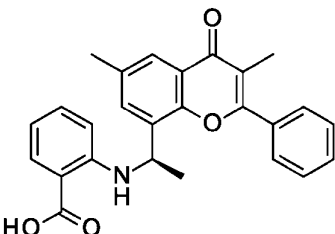
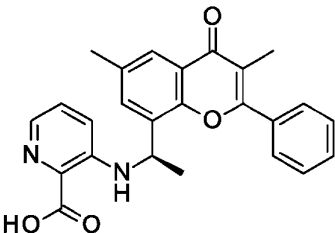
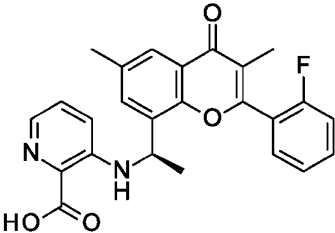
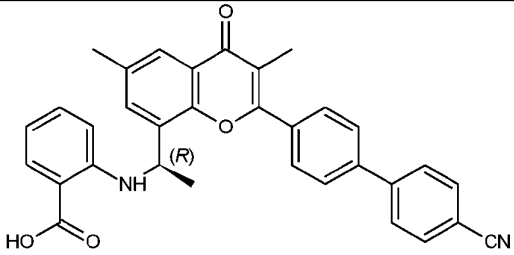
[778] List of Tested Compounds

[779] Table C lists the compounds tested in the experiments below. Compounds 1, 21, 36, 93, and 172 correspond to Example 1, 21, 36, 93, and 172 above. Compound N1, Compound N2, Compound N3, Compound N4, Compound N5, and Compound N6 are described in WO2021/202964, the content of which is incorporated herein by reference in its entirety with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein. Compound HP0, Compound HP1, Compound HP2, and Compound HP3 are described in WO2021/222556, the content of which is incorporated herein by reference in its entirety with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein. Compound HP4, HP5, and HP6 are described in WO2022/265993, the content of which is incorporated herein by reference in its entirety with respect to the PI3K α inhibitor compounds and methods of making and using the PI3K α inhibitor compounds disclosed therein.

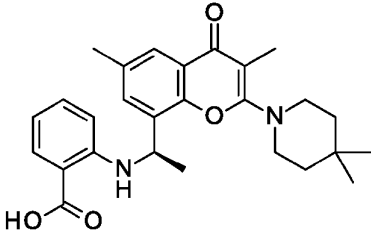
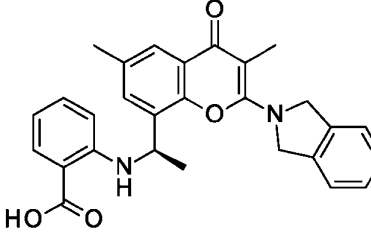
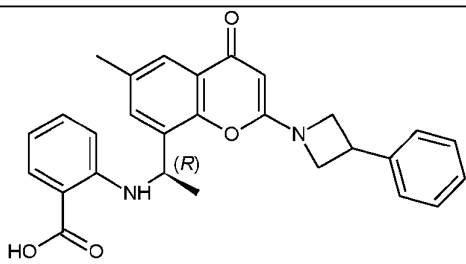
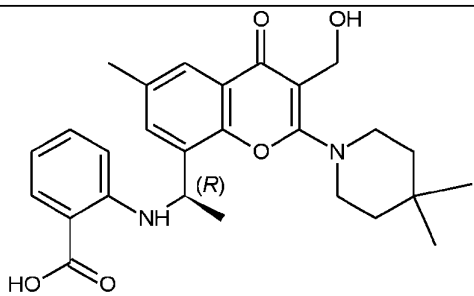
[780] Table C. List of Tested Compounds

<u>Compound</u>	<u>Structure</u>
Alpelisib	
Inavolisib (GDC-0077)	

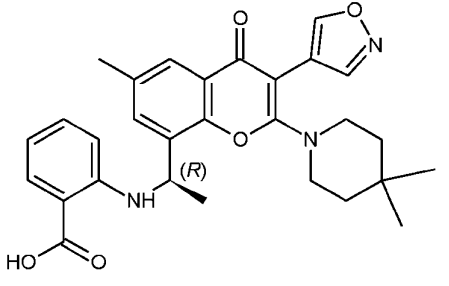
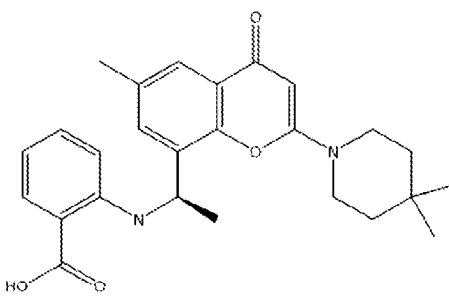
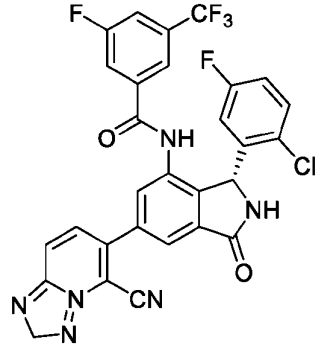
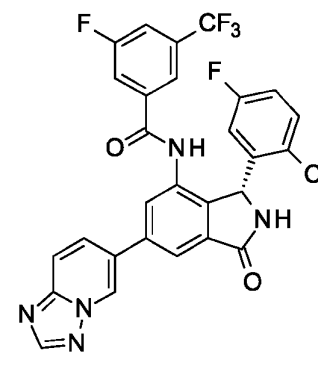
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Compound 1	
Compound 21	
Compound 36	
Compound 93	
Compound 172	

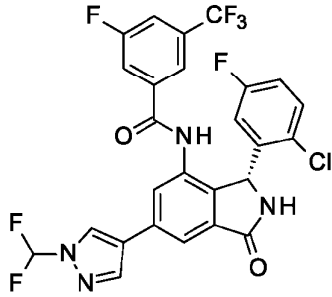
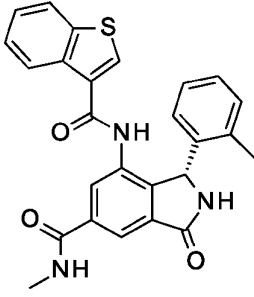
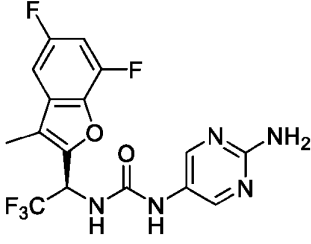
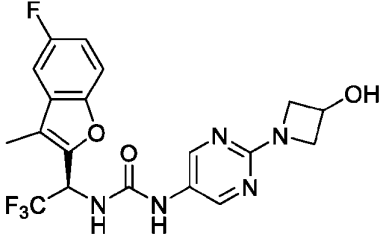
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Compound N1	
Compound N2	
Compound N3	
Compound N4	

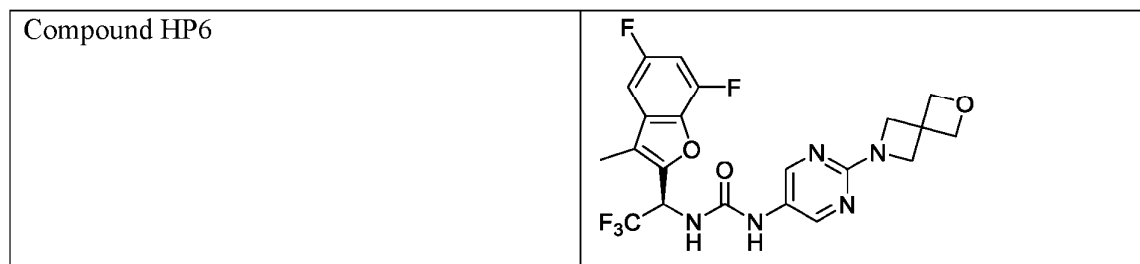
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Compound N5	 <p>Chemical structure of Compound N5: A chromone derivative. The chromone core has a methyl group at position 6 and a 1,3,4-oxadiazol-5-yl group at position 2. At position 3, there is a (R)-1-((4-carboxyphenyl)amino)ethyl group, indicated by a wedge bond. At position 4, there is a 1-(4,4-dimethylpiperidin-1-yl) group.</p>
Compound N6	 <p>Chemical structure of Compound N6: A chromone derivative. The chromone core has a methyl group at position 6 and a 1,3,4-oxadiazol-5-yl group at position 2. At position 3, there is a (R)-1-((4-carboxyphenyl)amino)ethyl group, indicated by a wedge bond. At position 4, there is a 1-(4,4-dimethylpiperidin-1-yl) group.</p>
Compound HP0	 <p>Chemical structure of Compound HP0: A benzimidazole derivative. The benzimidazole core has a cyano group at position 2 and a 4-(4-(trifluoromethyl)-2-fluorophenyl)phenyl group at position 6. At position 4, there is a 1-((4-chloro-2-fluorophenyl)amino)ethyl group, indicated by a dashed bond. At position 5, there is a 1-((4-(trifluoromethyl)-2-fluorophenyl)amino)ethyl group, indicated by a wedge bond.</p>
Compound HP1	 <p>Chemical structure of Compound HP1: A benzimidazole derivative. The benzimidazole core has a cyano group at position 2 and a 4-(4-(trifluoromethyl)-2-fluorophenyl)phenyl group at position 6. At position 4, there is a 1-((4-chloro-2-fluorophenyl)amino)ethyl group, indicated by a dashed bond. At position 5, there is a 1-((4-(trifluoromethyl)-2-fluorophenyl)amino)ethyl group, indicated by a wedge bond.</p>

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Compound HP2	
Compound HP3	
Compound HP4	
Compound HP5	

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[781] *In vitro* signaling assay for PI3K α substrates

[782] An *in vitro* signaling assay for PI3K α substrates such as p-AKT and p-S6 may be performed as follows. Cells are cultured and seeded into 60mm dishes. Dishes are incubated at 37 °C overnight allowing cells to be attached on the dish bottom and 50-60% cell confluence was achieved at the time of treatment.

[783] Stock solutions of test compounds are diluted in DMSO and added into medium to make final working concentrations. Cell dishes are shaken slightly allowing compound to be distributed evenly and cells are incubated with compound at 37°C for 4 hours. Cells are treated with compounds successively in 3 min interval for each dish. Final DMSO% of each group is 0.04%.

[784] Buffers are prepared as follows.

[785] Lysis Buffer: 10 μ l Halt protease inhibitor cocktail is added into 1ml cell lysis buffer (1x working buffer).

[786] Electrophoresis Running Buffer: 50 ml 20 $\times$ Running Buffer are diluted into 1000 ml with ddH₂O.

[787] 1 $\times$ Transfer Buffer: Add 100 ml 20 $\times$ Transfer Buffer and 400 ml methanol into 1500 ml ddH₂O.

[788] 1 $\times$ TBST Buffer: 50 ml 20 $\times$ TBST Buffer are diluted into 1000 ml with ddH₂O.

[789] Blocking Buffer: 2.5 g blocker was dissolved into 50 ml 1 $\times$ TBST Buffer and stored at 4°C.

[790] Primary Antibody Dilution: All primary antibodies tested are diluted in blocking buffer at the ratio of 1:1000.

[791] Secondary Antibody Dilution: Anti-rabbit IgG, HRP-linked antibody are diluted with blocking

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buffer at the ratio of 1:2000.

[792] Chemiluminescence Reagent: Stable peroxide solution and the Luminol/Enhancer solution were mixed at 1:1 ratio to make final working ECL reagent.

[793] Cell proteins are extracted as follows. After treatment for indicated time, cells are washed gently by 5 mL ice-cold PBS once. PBS is aspirated completely and 120 μ L ice-cold complete lysis buffer (with Halt protease inhibitor) is added to each dish drop by drop. Cell lysates are collected by scraper and transferred to 1.5 ml pre-cold eppendorf tube. Lysates are vortexed for few seconds and kept on ice for 1 hour and vortexed every 15 min. Cell lysates are spun at 15000 rpm for 15 min at 4°C and clear lysates for each sample are collected and transferred to a new eppendorf tube without touching the pellet, and a small volume of supernatant (around 20 μ L) is left behind. The total amount of protein is quantified by performing a Bradford assay.

[794] A western blot is performed as follows. 15 μ g total protein is loaded on 4-12% Bis-Tris Mini gel and followed by gel electrophoresis at the constant voltage of 120V (Novex Xcell Surelock electrophoresis cell EI0001). Proteins are transferred to nitrocellulose membrane (Trans-Blot Turbo mini 0.2 μ m nitrocellulose transfer pack, BioRad 1704158) using BioRad Transblot Turbo transfer system (BioRad 17001918). After transferring, membrane is blocked by blocking buffer for 1h at RT. Blocked membrane is washed 3x 5min with 1xTBST and incubated with primary antibodies in 1x TBST with 5% BSA overnight at 4°C. Membrane is washed 3x 10min with 1x TBST and incubated with secondary antibody for 1 hour at RT. Membrane is washed 3x 10min with 1x TBST and target protein is detected with SuperSignal West Dura Extended Duration Substrate by using ProteinSimple FluorChem E imaging system.

[795] The intensity of the signal of interest is measured by Image J software. The signal intensity of the band is directly proportional to the concentration of target protein. The relative expression of the target protein is calculated by the ratio of target band intensity between treatment group and control group. The relative expression of the target protein for DMSO control group is set to 100. Relative protein expression = (target protein intensity in treatment group /target protein intensity in control group)*100.

[796] Establishment and Characterization of Cells Resistant to PIK3 α Specific Inhibitors

[797] The purpose of these experiments was to establish cell lines that had acquired resistance to treatment with PIK3 α specific inhibitors, including alpelisib (ALP-R), Compound 1 (Cpd-R), Compound 21 (Cpd 21-R), Compound N1 (Cpd N1-R) and Compound N2 (Cpd N2-R). Control cells lines were naïve cells treated with vehicle (DMSO).

[798] Three cell lines were utilized to generate resistant cell lines: i) MDA-MB-453 cells (H1047+/-, TNBC, H0147:WT=2:1); ii) SUM185PE cells (H1047+/-, TNBC); and T47D cells (H1047R+/-, ER+, HER2-, H1047:WT=5:1) cells.

[799] i). Resistant MDA-MB-453 cells. Low passage MDA-MB-453 cells (H1047+/-, TNBC, H0147:WT=2:1) were kept in poly-D lysine-coated plates and subjected to continuous compound selection starting with a cell titer glow (CTG) cell proliferation EC₅₀ dose until resuming a stable proliferation rate.

[800] Compound concentrations (alpelisib, Compound 1, Compound 21, Compound N1, and Compound N2) were gradually increased over several months to achieve low, medium, or high levels of resistance in full serum medium, as follows: at 3 months to 2 μ M (low level of resistance); at 4 months to 5 μ M (medium level of resistance); and at 5 months to 10 μ M (high level of resistance). Cells were replenished with fresh selection medium every 3-4 days and were sub-cultured at 1:3 after confluency reached up to 70-80%. Levels of resistance were assessed by: EC₅₀ shift in growth inhibition measured by CTG assays; b. Changes in signaling inhibition assessed by Western blot analysis of phosphorylation; and c. Stability of the colony in selection-free conditions.

[801] Cells were considered resistant after achieving a log fold of EC₅₀ increase in the cell proliferation assay. In addition to cell proliferation, resistance was monitored by Western blotting to confirm PI3K pathway modulation. At the end of the selection process cell line authenticity was confirmed by short tandem repeat (STR) analysis.

[802] ii). Resistant SUM185PE cells. Cells selected for acquired resistance to Compound 1 were developed using SUM185PE (H1047+/-, TNBC) parental cells. Cells were continuously exposed to increasing concentrations of alpelisib, Compound 1, Compound 21, Compound N1, and Compound N2. Drug exposure was progressively doubled once the cells resumed a stable proliferation rate

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from EC₅₀ 30 - 50 nM to 10 μ M in full serum medium. Cells were replenished with fresh selection medium every 3-4 days and were sub-cultured at 1:3 once confluency reached up to 70-80%. Selected cells are cultured in 10 μ M of drug to maintain the resistant phenotype. For experimental characterization, the drug is removed for 48 h. At the end of the selection process cell line authenticity was confirmed by STR analysis. Fold resistance was calculated as EC₅₀ resistant cells / EC₅₀ parental cells (CTG).

[803] iii.). Resistant T47D cells. Cells having acquired resistance to Compound 1 or Compound 21 were developed similarly using T47D (H1047R+/-, ER+, HER2-, H1047:WT=5:1) parental cells.

[804] Testing for Cross-Resistance in MDA453 Cells

[805] The purpose of these experiments was to determine whether cells that had acquired resistance to the PI3K α specific inhibitors alpelisib or Compound 21 had cross-resistance to other PI3K α specific inhibitors in cell proliferation assays.

[806] MDA453 cells that are resistant to alpelisib (ALP-R) or Compound 21 (Cpd 21-R) were created as described above. The ALP-R cells and Cpd 21-R cells then were tested for cross-resistance by performing a cell proliferation assay in the presence of PIK3 α specific inhibitors including alpelisib, Compound 1, Compound 21, Compound 36, Compound 93, and Compound HP1 and calculating an EC₅₀ and fold change for ALP-R cells and Cpd 21-R cells relative to naïve MDA453 cells. The results for the cross-resistance experiments are provided in Table D. The cross-resistance cells demonstrated increased levels of resistance relative to naïve cells in varying degrees.

[807] Table D. EC₅₀ of Selected Compounds in Alpelisib Resistant MDA453 Cells (ALP-R) and Compound 21-Resistant MDA453 Cells

FBS-adjusted EC₅₀ (nM) (Fold-Change)	Alpelisib	Compound 1	Compound 21	Compound 36	Compound 93	Compound HP1
Naïve	147.0	0.9	1.4	1.8	1.1	23.5
ALP-R	11720.7 (80X)	479.6 (533X)	991.2 (708X)	20.6 (11X)	11.3 (10X)	926.0 (39X)

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Cpd 21-R	658.7 (4.5X)	14.7 (16X)	200.1 (143X)	13.8 (8X)	8.4 (8X)	235.6 (10X)

[808] Resistance Fold Change

[809] The purpose of these experiments was to determine a fold-change in resistance to PI3K α specific inhibitors for MDA453 cells that had acquired resistance to alpelisib, Compound 1, Compound 21, Compound N1, and Compound N2 relative to naïve MDA453 cells.

[810] MDA453 cells that were resistant to alpelisib (ALP-R), Compound 1 (Cpd 1-R), Compound 21 (Cpd 21-R), Compound N1 (Cpd N1-R), and Compound N2 (Cpd N2-R) were generated as described above. A fold-change in resistance was determined by challenging the resistant cells with alpelisib, inavolisib, Compound 1, Compound 21, Compound 36, and Compound HP and determined EC₅₀ values and fold-change in resistance. The results are presented in Table E.

[811] Table E. Fold-Change in Resistance for PI3K α specific inhibitors in MDA-MB-453 cells that are Resistant to alpelisib (ALP-R), Compound 21 (Cpd 21-R), Compound 1 (Cpd 1-R), Compound N1 (Cpd N1-R), and Compound N2 (Cpd N2-R) versus naïve MDA-MB-453 cells.

Fold-Change	Alpelisib	Inavolisib	Cpd 1	Cpd 21	Cpd N1	Cpd N2	Cpd 36	Cpd HP1
ALP-R	72.5	787.9	830.6	846.6	220.0	55.1	12.9	28.0
Cpd 21-R	4.8	9.7	7.9	58.4	45.1	56.2	9.0	4.3
Cpd 1-R	17.9	246.8	68.9	241.9	152.4	47.2	19.8	17.1
Cpd N1-R	2.0	2.2	14.5	120.8	102.2	64.7	8.0	2.6
Cpd N2-R	1.3	1.4	2.8	29.2	23.0	51.8	5.7	1.1
DMSO	1.7	1.7	1.0	1.0	1.2	1.0	1.5	1.2
Naive	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

[812] Stability of Resistance Phenotype

[813] The purpose of these experiments was to identify to assess the stability of resistance for MDA453 cells that had acquired resistance to Compound 21 (Cpd 21-R) and MDA453 cells that had acquired resistance to alpelisib (ALP-R) over passage of time. Cpd 21 or alpelisib was removed

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from the growth media for Cpd 21-R MDA453 cells and ALP-R MDA453 cells and resistance was assessed on day 3, day 10, and day 22. No substantial change in resistance levels in Cpd 21-R MDA453 cells and ALP-R MDA453 cells was observed 22 days after the Cpd 21 or alpelisib, respectively, was removed from the cells.

[814] Whole Genome Exome Sequencing of Resistant Cells to Identify Acquired Mutations in Cells with Acquired Resistance to Compound 21 or Compound 1

[815] The purpose of these experiments was to identify acquired mutations in cell lines that had acquired resistance to Compound 21 or Compound 1.

[816] Whole exome sequencing of MDA453 cells that had acquired resistance to Compound 21 (Cpd 21-R) and SUM185PE cells that had acquired resistance to Compound 1 (Cpd 1-R) was performed using Agilent SureSelect Human All Exon V7 plus UTR custom capture kit for each resistant cell model and its corresponding parental cell line. 200ng of DNA each was used for library generation. Qualitative and quantitative analysis of the sequencing libraries were performed with Fragment Analyzer and KAPA Library Quantification Kits, respectively. Libraries were multiplexed and then sequenced on the Illumina NovaSeq 6000 System to generate a minimum of 150M paired 150bp reads.

[817] Mutations in PIK3CA in addition to H1047R were identified in the MDA453 (Cpd 21-R) cells and the SUM185PE (Cpd 1-R) cell lines, including M1043I in the MDA453 (Cpd 21-R) cells and C901F in the SUM185PE (Cpd 1-R) cells. For the M1043I mutation, it was possible to determine its *in cis* occurrence with the H1047R mutation.

[818] Generation of H1047R+M1043I T47D Cells and Assessment of Resistance to PI3K α specific inhibitors

[819] The purpose of these experiments was to generate homozygous H1047R+M1043I T47D cells in a naïve background in order to test whether the M1043I mutation in *cis* with the H1047R was sufficient for conferring resistance to PI3K α specific inhibitors.

[820] Homozygous T47D cells with 6 copies of H1047R+M1043I were generated (T47D HM-6X).

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The T47D HM-6X cells then were tested for resistance to alpelisib, inavolisib (i.e., GDC-0077), Compound 1, Compound 21, Compound 36, Compound 93, Compound N1, Compound N2, inavolisib, and Compound HP1 after low passage and high passage.

[821] The results for the low passage T47D HM-6X cells are provided in Figs. 2-7 and Table F, and the results for the high passage T47D HM-6X cells are provided in Figs. 8-11. The results illustrate that the M1043I mutation in *cis* with the H1047R mutation resulted in enhanced resistance to PI3K α specific inhibitors relative to naïve cells.

[822] Table F. EC₅₀ of Selected Compounds in T47D (H1047R+M1043I)(6x) Cells in a CTG Cell Proliferation Assay

FBS-adjusted EC₅₀ (nM) in CTG Assay (Fold-Change)	Alpelisib	Compound 21	Compound 1	Compound 36	Compound 93	Compound HP1
Naïve	105.7	1.6	1.2	0.9	0.8	16
H1047R+M1043I-6X	258.2 (2.4×)	133.9 (85×)	9.7 (8.3×)	17.7 (19×)	11 (14×)	29.3 (1.8×)

[823] Generation of MCF-10A Cells Overexpressing H1047R in Conjunction with M1043I

[824] The purpose of these experiments was to generate MCF-10A cells that overexpress PI3K α having the M1043I mutation in *cis* with the H1047R mutation to determine whether the M1043I mutation in *cis* with the H1047R was sufficient for conferring resistance to PI3K α specific inhibitors.

[825] MCF-10A cells were transfected with vectors that overexpress H1047R or H1047R + M1043I. The MCF-10A(H1047R) cells and the MCF-10A(H1047R+M1043I) cells thus generated then were tested for resistance to alpelisib, inavolisib, Compound 1, Compound 21, Compound N1, Compound N2, and Compound HP1 in a cell proliferation assay. The results are presented in Table G and demonstrate that the MCF-10A(H1047R+M1043I) cells were more resistant to PI3K α specific inhibitors than MCF-10A(H1047R) cells.

[826] Table G. EC₅₀ of PI3K α specific inhibitors in MCF-10A (H1047R+M1034I) Cells Versus MCF-10A (H1047R) Cells

FBS-adjusted EC ₅₀ (nM)	Alpelisib	Inavolisib	Cpd 1	Cpd 21	Cpd N1	Cpd N2	Cpd HP1
H1047R	588.2	68.5	2.5	10.3	73.2	60.9	297.3
H1047R+M1034I	923.7	100.8	24.4	795.9	4356.0	4302.4	249.0
Fold Change	1.6×	1.5×	9.9×	77.0×	59.5×	70.6×	0.8×

[827] Effect of Combinations of PI3KCA inhibitors in T47D cells and T47D HM-6X cells *in vitro*

[828] T47D cells and T47D HM-6X cells (prepared as described above) were grown in the presence of increasing concentrations of a combination of two different pairs of inhibitors: 1) Compound 21 (six increasing concentrations: 0.004, 0.012, 0.037, 0.11, 0.33, and 1 μ M) and alpelisib (four increasing concentrations: 0.0333, 0.099, 0.297, 0.9 μ M); and 2) Compound 21 (six increasing concentrations: 0.004, 0.012, 0.037, 0.11, 0.33, and 1 μ M) and Compound HP1 (four increasing concentrations: 0.0333, 0.099, 0.297, 0.9 μ M). Relative growth inhibition was assessed in a cell proliferation assay (CTG). Dose-response matrices then were utilized together with Lowe model analysis and CompuSyn software to generate a combination index (CI) and assess synergy (CI<0.5 (LogCI < -0.3), additivity (CI between 0.5 and 2) (LogCI -0.3 – 0.3), and antagonism (CI>2.0 (LogCI> 0.3). Results are presented in Figs. 12-15.

[829] Effect of Combinations of PI3KCA inhibitors in MDA453 cells and MDA453 (Cpd 21-R) cells *in vitro*

[830] MDA453 cells and MDA453 (Cpd 21-R) cells (prepared as described above) were grown in the presence of increasing concentrations of a combination of two different pairs of inhibitors: 1) Compound 21 (six increasing concentrations: 0.004, 0.012, 0.037, 0.11, 0.33, and 1 μ M) and alpelisib (four increasing concentrations: 0.0333, 0.099, 0.297, 0.9 μ M); and 2) Compound 21 (six increasing concentrations: 0.004, 0.012, 0.037, 0.11, 0.33, and 1 μ M) and Compound HP1 (four increasing concentrations: 0.0333, 0.099, 0.297, 0.9 μ M). Relative growth inhibition was assessed in a cell proliferation assay (CTG). Dose-response matrices then were utilized together with Lowe

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model analysis and CompuSyn software to assess synergy ($CI < 0.5$ ($\text{LogCI} < -0.3$), additivity (CI between 0.5 and 2) ($\text{LogCI} -0.3 - 0.3$), and antagonism ($CI > 2.0$ ($\text{LogCI} > 0.3$)). Results are presented in Figs. 16-19.

[831] X-ray Structure and Binding Analysis

[832] The purpose of these experiments was to study the interaction of PI3K α specific inhibitors in PI3K α allosteric pocket 1 and PI3K α allosteric pocket 2 and to identify amino acid residues that interact with PI3K α specific inhibitors.

[833] X-ray structures and binding analyses were completed for Compound 21, Compound 192, Compound N3, Compound N4, Compound N5, Compound HP1, Compound HP2, and Compound N6. Compound structures and results are provided in Figs. 20-27. The results indicate that there are two allosteric pockets in PI3K α , which may be referred to as “PI3K α allosteric pocket 1” and “PI3K α allosteric pocket 2.” Compounds that bind PI3K α allosteric pocket 1 may interact with amino acid residues that include C901, T908, F909, H931, F954, Q981, Y985, Y1021, and R1047. Compounds that bind PI3K α allosteric pocket 2 may interact with amino acid residues that include L911, F937, F1002, E1012, and D1018. Fig. 27 illustrates binding of Compound N6 in PI3K α allosteric pocket 1 and concurrent binding of Compound HP2 in PI3K α allosteric pocket 2.

[834] Effect of a Combination of Compound 21 with Alpelisib or Inavolisib in a Cell Proliferation Assay *in vitro*

[835] The purpose of this experiment was to examine the effect of a combination of Compound 21 and alpelisib or a combination of Compound 21 and inavolisib in T-47D cells in a cell proliferation assay *in vitro*.

[836] Cells were seeded at an appropriate density in 20 μL volume of media into a clear bottom 384-well cell culture plate. Seeding density and culture medium details for each cell line are described in Table H. Plates then are incubated at 37 °C and 5% CO₂ and treated with test compound 24 hours post-seeding.

[837] Table H. Cell proliferation assay cell line information

Cell Line	Seeding density	Commercial reference	Culture Medium	Reading time (hours)
T-47D	1000	ATCC-HTB-133	RPMI 1640 media (Gibco A1049101), 10% h.i. FBS, and 1% penicillin-streptomycin	96

[838] Compounds were prepared as 10 mM DMSO stock solutions and used for dose-response studies. For combination treatments, two compounds were tested together at a fixed ratio with top starting concentrations of 10 μ M:10 μ M for Compound 21 and alpelisib or Inavolisib, while for single treatments, the starting concentration was 20 μ M. For both single and combination treatments, 1:3 serial dilutions were prepared in a 10-points concentration response curve (CRC) by using an acoustic liquid handler system (Echo 550 series instrument, Labcyte). A 5 $\times$ intermediate compound plate was generated in medium before adding compounds to the cells. Cells were treated with 5 μ L of serially diluted compounds, giving a final DMSO concentration of 0.2%. Staurosporine 2 μ M was used as a reference compound for the minimum signal and DMSO 0.2% as the maximum signal. Cell plates were incubated at 37 °C and 5% CO₂. After incubation with compounds for two cell doubling times, plates were removed from the incubator and 65 μ L of ice-cold EtOH 96% were added to each well to have a final EtOH 70%. After 30 minutes, media was removed and 20 μ L of PBS containing RNase (50 μ g/mL) and propidium iodide (1 μ g/mL) were added per well. Plates were sealed and incubated 1 hour at room temperature (preserved from light) and then scanned with an ACUMEN EXPLORER™ [Laser-scanning fluorescence microplate cytometer manufactured by TTP LABTECH LTD]. For those cell lines growing as aggregates, total area population or total PI intensity were used to evaluate total cell number, otherwise number of objects was used as standard readout. Results are provided in Table I.

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[839] Table I. Combination results for cell proliferation assay

Cell line	Treatment 1	Treatment 2	Combination Index 50, 60 and 70 (CI50, CI60, CI70)	Average Biological interpretation	Genetic Background
T47D	Cpd 21	Alpelisib	0.77, 0.80, 0.79	Additive	ER+, HER2- (PIK3CA H1047R)
		GDC-0077	0.63, 0.63, 0.60	Additive	

N=4 replicate. Ratios Compound 21-Alpelisib/GDC-0077 were 10:10

[840] Effect of *in vivo* combination of Compound 21, Alpelisib, and Fulvestrant in an ER-positive, PI3Kα H1047R +/- breast cancer xenograft tumor model implanted in mice

[841] The purpose of the following xenograft tumor inhibition assay was to measure reduction in tumor volume and combination effect in response to test Compound 21 administration alone, and in combination with low doses of PI3K alpha orthosteric inhibitor alpelisib with/without the estrogen receptor degrader (SERD) fulvestrant.

[842] T-47D (ATCC #HTB-133) were expanded in culture, harvested and injected 5×10^6 cells in 1:1 HBSS+MATRIGEL™ solution (200 uL) subcutaneously onto the rear right flank of female NOD scid gamma (NSG) mice (The Jackson Laboratory, Inc). Twenty-four hours prior to implantation of cells, estrogen pellets were implanted (0.72 mg/pellet, 17β estradiol, 90-day release, Innovative Research) subcutaneously. Tumor growth and body weight were measured twice per week beginning the seventh day after the implantation. When tumor sizes reached 250-300 mm³, animals were randomized into groups of 5 animals. Compound 21 was prepared in an appropriate vehicle (1 molar equivalent of 1N NaOH in DI water) and administered by oral gavage for 28 days, BID. The PI3Kα orthosteric inhibitor alpelisib was prepared in an appropriate vehicle (10% 2-Hydroxypropyl-β-Cyclodextrin in Sterile Water)) and administered by oral gavage for 28 days, QD. The estrogen receptor degrader fulvestrant (formulated by the supplier) was administered Q7D for 28 days. Groups and treatments are defined in Table J. Tumor response was determined by tumor volume measurement performed twice a week during treatment. Body weight measurement were taken as a general measure of toxicity whenever tumor volume was measured.

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[843] Compound 21 is found to have improved efficacy for reduction in tumor size when combined with low dose alpelisib with or without fulvestrant in the ER-positive human breast cancer xenograft model T47D as provided in Table K and Fig. 28 and Fig. 29. Statistical analyses of the combination of Compound 21 with low doses of alpelisib or fulvestrant and the triple combination of compound of Compound 21 and low doses alpelisib plus fulvestrant in the ER-positive human breast cancer xenograft model in mice (as defined by the Bliss Independence method) indicate that Compound 21 demonstrates additive and greater than effect in combinations as shown in Table L.

Table J. In vivo efficacy study: compound and dosing information

Group #	Drug	N	Dose (mg/kg)	Route	Frequency	Duration
1	Vehicle	5	-	p.o.	BID	28 days
2	Compound 21	5	37.5mg/kg	p.o.	BID	28 days
3	Alpelisib	5	6.25mg/kg	p.o.	QD	28 days
4	Alpelisib	5	12.5mg/kg	p.o.	QD	28 days
5	Fulvestrant	5	5mg/animal	i.v.	Q7D	28 days
6	Compound 21 + Fulvestrant	5	37.5mg/kg 5mg/animal	p.o. i.v.	BID Q7D	28 days
7	Compound 21 + Alpelisib	5	37.5mg/kg 6.25mg/kg	p.o. p.o.	BID QD	28 days
8	Compound 21 + Alpelisib	5	37.5mg/kg 6.25mg/kg	p.o. p.o.	BID QD	28 days

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9	Compound 21 + Alpelisib	5	37.5mg/kg 6.25mg/kg	p.o. p.o.	BID QD	28 days
10	Compound 21 + Alpelisib	5	37.5mg/kg 12.5mg/kg	p.o. p.o.	BID QD	28 days
11	Alpelisib + Fulvestrant	5	6.25mg/kg 5mg/animal	p.o. i.v.	QD Q7D	28 days
12	Alpelisib + Fulvestrant	5	12.5mg/kg 5mg/animal	p.o. i.v.	QD Q7D	28 days

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Table K. In vivo efficacy study: mean tumor volume and percent of response

Group	Mean Tumor Volumes (mm ³)					Obs - EAR (mm ³)	Percent Response (D[T/C] % or Reg%)			
	Vehicle	1 st Cpd	2 nd Cpd	3 rd Cpd	Combination	EAR	1 st Cpd	2 nd Cpd	3 rd Cpd	Combination
Compound 21 37.5 mg/kg + Fulvestrant 5 mg/animal	694.3	300.3	365.6	.	105.2	158.1	9.3	24.3	.	-59.5
Compound 21 37.5 mg/kg + Alpelisib 6.25 mg/kg	695.4	300.3	591.7	.	237.2	255.5	10.8	76.6	.	-6.0
Compound 21 37.5 mg/kg + Alpelisib 12.5 mg/kg	695.7	300.3	533.2	.	142.6	230.1	9.8	62.9	.	-44.6
Alpelisib	695.5	591.7	365.6	.	274.7	311.0	76.4	24.9	.	4.2

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Table L. In vivo efficacy study: pairwise comparisons and Bliss Independence effect

Group	Pairwise Comparison p-values				Bliss Effect Estimate (log ₁₀)	Bliss Effect SE (log ₁₀)	Bliss Effect p-value	Combination Effect Result
	Vehicle vs Comb.	1 st Cpd vs Combination	2 nd Cpd vs Combination	3 rd Cpd vs Combination				
Compound 21 37.5 mg/kg + Fulvestrant 5 mg/animal	< 0.001*	< 0.001*	< 0.001*	.	-0.088	0.038	0.022*	Greater Than Additive
Compound 21 37.5 mg/kg + Alpelisib 6.25 mg/kg	< 0.001*	0.0825*	< 0.001*	.	-0.016	0.042	0.6991	No Effect
Compound 21 37.5 mg/kg + Alpelisib 12.5 mg/kg	< 0.001*	< 0.001*	0.0247*	.	-0.104	0.040	0.0116*	Greater Than Additive
Alpelisib 6.25 mg/kg + Fulvestrant 5 mg/animal	< 0.001*	< 0.001*	< 0.001*	.	-0.027	0.038	0.4790	Additive
Alpelisib	< 0.001*	< 0.001*	< 0.001*	.	-0.053	0.035	0.1285	Additive

12.5 mg/kg + Fulvestrant 5 mg/animal										
Compound 2l 37.5 mg/kg + Apalisib 6.25 mg/kg + Fulvestrant 5 mg/animal	<0.001*	<0.001*	<0.001*	<0.001*	-0.352	0.110	0.0017*			Greater Than Additive
Compound 2l 37.5 mg/kg + Apalisib 12.5 mg/kg + Fulvestrant 5 mg/animal	<0.001*	<0.001*	<0.001*	<0.001*	-0.303	0.101	0.0031*			Greater Than Additive

* ; significant ($p < 0.05$)

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[845] Effect of *in vivo* combination of Compound 21 and Alpelisib in a TNBC, PI3Ka H1047R -/+ breast cancer xenograft tumor model implanted in mice and analysis of C-peptide and insulin levels

[846] The purpose of the following xenograft tumor inhibition assay was to measure reduction in tumor volume and combination effect in response to test Compound 21 administration alone, and in combination with low doses of alpelisib. The purpose of the assay also was to measure C-peptide levels and insulin levels in response to test Compound 21 administration alone, and in combination with low doses of alpelisib.

[847] MDA-MB-453(ATCC #HTB-131) were expanded in culture, harvested and injected 1×10^7 cells in 1:1 HBSS+MATRIGEL™ solution (200 uL) subcutaneously on to the rear right flank of female NOD scid gamma (NSG) mice (The Jackson Laboratory, Inc). Tumor growth and body weight were measured twice per week beginning the seventh day after the implantation. When tumor sizes reached 250-300 mm³, animals were randomized into groups of 5 animals. Compound 21 was prepared in an appropriate vehicle (1 molar equivalent of 1N NaOH in DI water) and administer by oral gavage for 24 days, BID. The Pi3Kalpha orthosteric inhibitor alpelisib was prepared in an appropriate vehicle (10% 2-Hydroxypropyl-β-Cyclodextrin in Sterile Water) and administered by oral gavage for 24 days, QD. Groups and treatments are shown in Table M. Tumor response was determined by tumor volume measurement performed twice a week during treatment. Body weight measurement were taken as a general measure of toxicity whenever tumor volume was measured. C-peptide and insulin and levels were measured at the time of collection and shown in Table N and Table O.

[848] Compound 21 is found to have improved efficacy for reduction in tumor size when combined with low doses of alpelisib in the human triple negative MDA-MB-453 breast cancer as provided in Table P. Statistical analyses of the combination of compound of Compound 21 with low doses of alpelisib in the triple negative human breast cancer xenograft model in mice (as defined by the Bliss Independence method) indicate that the Compound 21 demonstrates additive and greater than additive effect in combinations as shown in Table Q.

[849] Table M. In vivo efficacy study: compound and dosing information

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Group #	Drug	N	Dose (mg/kg)	Route	Frequency	Duration
1	Vehicle	5	-	p.o.	BID	24 days
2	Compound 21	5	37.5mg/kg	p.o.	BID	24 days
3	Compound 21	5	75mg/kg	p.o.	BID	24 days
3	Alpelisib	5	6.25mg/kg	p.o.	QD	24 days
5	Alpelisib	5	12.5mg/kg	p.o.	QD	24 days
6	Compound 21	5	37.5mg/kg	p.o.	BID	24 days
	+ Alpelisib		6.25mg/kg	p.o.	QD	
7	Compound 21	5	37.5mg/kg	p.o.	BID	24 days
	+ Alpelisib		12.5mg/kg	p.o.	QD	
8	Compound 21	5	75mg/kg	p.o.	BID	24 days
	+ Alpelisib		6.25mg/kg	p.o.	QD	
9	Compound 21	5	75mg/kg	p.o.	BID	24 days
	+ Alpelisib		12.5mg/kg	p.o.	QD	

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Table N. C-peptide measurements at the end of the study

C-peptide (ng/ml)	Vehicle	Cpd 21 37.5 mg/kg BID	Cpd 21 37.5 mg/kg BID	Cpd 21 37.5 mg/kg BID	Alpelisib 12.5mg/kg QD	Cpd 21 37.5 mg/kg BID +Alpelisib 6.25mg/kg QD	Cpd 21 37.5 mg/kg BID +Alpelisib 12.5mg/kg QD	Cpd 21 75mg/kg BID +Alpelisib 12.5mg/kg QD
Mouse 1	0.875	0.781	0.334	0.378	1.522	0.927	0.711	2.305
Mouse 2	0.305	0.785	0.305	0.499	1.07	0.781	1.164	1.044
Mouse 3	0.444	1.074	0.577	0.752	0.496	1.002	1.229	1.063
Mouse 4	0.253	0.444	0.536	0.279	0.741	0.867	0.867	1.278
Mouse 5	0.836	0.463	1.369	0.144	0.44	0.744	0.785	0.703
MEAN	0.5406	0.7094	0.6242	0.4104	0.8538	0.8642	0.9512	1.2786

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Table O. Insulin measurements at the end of the study

Insulin (ng/ml)	Vehicle	Cpd 21 37.5 mg/kg BID	Cpd 21 37.5 mg/kg BID	Alpelisib 6.25mg/kg QD	Alpelisib 12.5mg/kg QD	Cpd 21 37.5 mg/kg BID +Alpelisib 6.25mg/kg QD	Cpd 21 37.5 mg/kg BID +Alpelisib 12.5mg/kg QD	Cpd 21 75mg/kg BID +Alpelisib 6.25mg/kg QD	Cpd 21 75mg/kg BID +Alpelisib 12.5mg/kg QD
Mouse 1	1.0082	0.9949	0.7134	0.3478	1.7096	0.8593	1.0001	1.3157	1.6667
Mouse 2	0.6552	1.1809	0.2226	0.4345	1.9572	0.8603	0.9845	0.7867	0.7965
Mouse 3	0.6216	1.6987	0.9559	0.6773	0.6956	1.2304	1.7329	0.8206	1.0286
Mouse 4	0.3859	0.7860	0.6035	0.1739	0.4809	1.2150	1.0296	0.8082	1.3162
Mouse 5	0.9477	0.5451	1.2551	0.4014	1.2112	0.9758	0.8369	1.1601	0.8719
MEAN	0.7237	1.0411	0.7501	0.4070	1.2109	1.0281	1.1168	0.9783	1.1360

Table P. In vivo efficacy study: mean tumor volume and percent of response

Group	Mean Tumor Volumes (mm ³)					Obs - EAR (mm ³)	Percent Response (D[T/C]% or Reg%)		
	Vehicle	1 st Cpd	2 nd Cpd	Comb.	EAR		1 st Cpd	2 nd Cpd	Comb.
Compound 21 37.5 mg/kg + Alpelisib 6.25 mg/kg	516.4	283.0	445.3	179.2	244.0	-64.8	5.6	71.2	-33.4
Compound 21 37.5 mg/kg + Alpelisib 12.5 mg/kg	516.4	283.0	391.8	163.1	214.7	-51.6	6.8	50.3	-38.7
Compound 21 37.5 mg/kg + Alpelisib 6.25 mg/kg	516.4	167.1	445.3	105.7	144.1	-38.3	-37.5	71.5	-60.4
Compound 21 37.5 mg/kg + Alpelisib 12.5 mg/kg	516.4	167.1	391.8	56.8	126.8	-70.0	-34.9	52.1	-77.8

[850] For Table P, analysis for tumor volume is based on Log 10 and SpatialPower covariance structure. Delta T/C% is calculated when the endpoint tumor volume in a treated group is at or above baseline tumor volume. The formula is $100 \times (T - T_0) / (C - C_0)$, where T and C are mean endpoint tumor volumes in the treated or control group, respectively. T_0 and C_0 are mean baseline tumor volumes in those groups. Regression% is calculated when the endpoint volume is below baseline. The formula is $100 \times (T - T_0) / T_0$, where T_0 is the mean baseline tumor volume for the treated group. Grand mean of all groups from baseline (randomization) is used to

compute % change of T/C. EAR is the Expected additive response tumor volume. Tumor volumes measured after 24 days treatment.

Table Q. In vivo efficacy study: pairwise comparisons and Bliss Independence effect

Combination	Pairwise Comparison p-values			Bliss Effect Estimate (log ₁₀)	Bliss Effect SE (log ₁₀)	Bliss Effect p-value	Comb. Effect Result
	Vehicle vs Comb.	1 st Cpd vs Comb.	2 nd Cpd vs Comb.				
COMPOUND 21 37.5 mg/kg + Alpelisib 6.25 mg/kg	< 0.001*	0.0108*	< 0.001*	-0.067	0.053	0.2098	Additive
COMPOUND 21 37.5 mg/kg + Alpelisib 12.5 mg/kg	<0.001*	0.0057*	< 0.001*	-0.060	0.058	0.3089	Additive
COMPOUND 21 75 mg/kg + Alpelisib 6.25 mg/kg	< 0.001*	0.0022*	< 0.001*	-0.067	0.044	0.1319	Additive
COMPOUND 21 75 mg/kg + Alpelisib 12.5 mg/kg	< 0.001*	< 0.001*	< 0.001*	-0.174	0.042	< 0.001*	Greater Than Additive

*: significant (p<0.05)

[851] Additional Methods

[852] Data Analysis and Interpretation of Combination Effect. The Loewe method was used to calculate an *in vitro* combination effect (L. Zhao, et al, Front Biosci, 2010, 2:241-249 and L. Zhao, et al, Clin Cancer Res, 2004, 10(23):7994-8004). To identify synergistic or antagonistic interactions between two drugs, a curve shift analysis following Loewe model was performed using a customized Genedata module. Single agent's curves were adjusted using 4 parameters logistic regression. Criteria and restrictions used for the fitting were (i) bottoms $< (-20)$ are fixed to 0 and (ii) top > 120 fixed to 100. If all the observations were lower than a threshold set by the user, then a constant fit with hill = 0 was performed and the IC_{50} was considered higher than the maximum included concentration. Once the absolute IC_{50} of each single agent was obtained, the equivalent concentration at 50% of activity was calculated for the singles and combination. Using these equivalent concentrations together with the measured activities, an absolute IC_{50} was calculated. The curve for single agents will reach 50% activity at values of eq concentrations equals to 1, while synergistic combinations will reach the 50% at lower values resulting in a leftward shift, and antagonistic combination will show rightward shift. Equivalent concentrations also were used to calculate CI_{50} (Combination Index at 50% of activity), where CI_{50} equals absolute IC_{50} of combination curve. Together with CI_{50} other CI's (Combination Indexes) at different percentages of activity can be calculated (CI_{10} , CI_{20} , CI_{30} , CI_{40} , CI_{60} , CI_{70} , CI_{80} , CI_{90}). To calculate CI_{Inn} , equivalent concentrations at different activity percentages were calculated. For each activity percentage, the margin of error was calculated and was equivalent to the confidence interval at 95%. Using this confidence interval, the upper limit was calculated as the addition of margin of error to the CI and the lower limit as the subtraction of the margin of error to the CI. Upper limit = $CI + \text{Confidence interval } 95\%$ and Lower Limit = $CI - \text{Confidence interval } 95\%$. These limits were then used to interpret the results.

Statistical Interpretation at each activity percentage was as follows:

Lower limit < 1 and upper limit > 1	Additive
Upper limit < 1	Synergy

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Lower limit >1	Antagonist
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Biological Interpretation at each activity percentage is as follows:

$CI_{nn} < 0.5$	Synergy
$CI_{nn} > 0.5$ and $CI_{nn} < 2$	Additive
$CI_{nn} > 2$	Antagonist

[853] Combination Analysis Method for in vivo studies (Bliss Independence). The Bliss Independence method was used to estimate the tumor volume combination treatment effect. The $\log_{10}$ transformed tumor volume data for the control, single agent 1, single agent 2, and the combination of single agents 1 and 2 groups, were analyzed using the previously described RM ANOVA model with an added two-way interaction contrast of the following form to estimate the Bliss Effect:

$$\log_{10} \overline{TV}_{\text{Control}} - \log_{10} \overline{TV}_{\text{Single Agent 1}} - \log_{10} \overline{TV}_{\text{Single Agent 2}} + \log_{10} \overline{TV}_{\text{Combination}}$$

where

$\log_{10} \overline{TV}_t$ is the mean tumor volume for treatment t

[854] Assuming that tumor volumes can, in theory or in practice, reach zero (complete regression), this approach is mathematically equivalent to the Bliss Independence method when analyzing tumor volume on the log scale.

[855] If the combination effect is exactly additive, then by definition of Bliss Independence the two-way interaction contrast estimate equals zero. If the contrast estimate is statistically different from zero ($p \leq 0.05$), then the combination effect is either greater than (synergistic) or less than (antagonistic) additive if the observed combination mean volume is less than or greater than the *expected additive response* tumor volume (EAR_{TV}), respectively. The follow equation was used to estimate EAR_{TV}

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$$EAR_{TV} = \frac{\overline{TV}_{\text{Single Agent 1}} \times \overline{TV}_{\text{Single Agent 2}}}{\overline{TV}_{\text{Control}}}$$

[856] If the interaction contrast test and all pairwise comparisons between the control and each single agent treated group versus the combination treated group are all statistically significant ($p \leq 0.05$), and the observed combination mean volume is less than the EAR volume, then the combination effect is declared greater than additive (synergistic).

[857] If the interaction contrast test is statistically significant ($p \leq 0.05$) and the observed combination mean volume is greater than the EAR volume, then the combination effect is declared less than additive (antagonistic) regardless of the pairwise comparison results.

[858] If the interaction test is not statistically significant ($p \geq 0.05$), but all pairwise comparisons versus the combination group are significant ($p \leq 0.05$), then the combination effect is declared additive, otherwise the combination effect is inconclusive (no effect).

[859] It is important to note that the LS Means used for the combination analysis and reported output, were estimated from a RM ANOVA model consisting only the 4 groups related to each combination (i.e., control, single agent 1, single agent 2, and combination), and not by fitting each group separately as was done for the Tumor Growth Inhibition analysis. While the estimates are similar, they may not match exactly.

[860] Triple Combination Analysis. The tumor growth inhibition Bliss Independence triple combination analysis follows the same general methodology as previously described in the documentation of the Zeus Combination Analysis. The $\log_{10}$ transformed tumor volume data for the *control*, *single agent 1*, *single agent 2*, *single agent 3*, and the *triple combination* of the three single agents were analyzed using the RM ANOVA model previously described in the documentation of the Zeus Tumor Growth Inhibition Analysis. The *Bliss Effect* was estimated with contrast statement of the following form:

$$2 * \log_{10} \overline{TV}_{\text{Control}} - \log_{10} \overline{TV}_{\text{Single Agent 1}} - \log_{10} \overline{TV}_{\text{Single Agent 2}} - \log_{10} \overline{TV}_{\text{Single Agent 3}} \\ + \log_{10} \overline{TV}_{\text{Combination}}$$

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where

$\log_{10} \overline{TV}_t$ is the mean tumor volume for treatment t

[861] Assuming that tumor volumes can, in theory or in practice, reach zero (complete regression), this approach is mathematically equivalent to the Bliss Independence method when analyzing tumor volume on the log scale.

[862] If the combination effect is exactly additive, then by definition of Bliss Independence the contrast estimate equals zero. If the contrast estimate is statistically different from zero ($p \leq 0.05$), then the combination effect is either *greater than (synergistic)* or *less than (antagonistic) additive* if the observed combination mean volume is less than or greater than the *expected additive response* tumor volume (EAR_{TV}), respectively. The triple combination EAR_{TV} was calculated using the following equation:

$$EAR_{TV} = \frac{\overline{TV}_{\text{Single Agent 1}} \times \overline{TV}_{\text{Single Agent 2}} \times \overline{TV}_{\text{Single Agent 3}}}{\overline{TV}_{\text{Control}}^2}$$

[863] If the contrast is statistically different from zero ($p \leq 0.05$) and all pairwise comparisons between the control and each single agent treated group versus the combination treated group are all statistically significant ($p \leq 0.05$), and the observed combination mean volume is less than the EAR_{TV} , then the combination effect is declared *greater than additive (synergistic)*.

[864] If the contrast is statistically different from zero ($p \leq 0.05$) and the observed combination mean volume is greater than the EAR volume, then the combination effect is declared *less than additive (antagonistic)* regardless of the pairwise comparison results.

[865] If the interaction test is not statistically significant ($p > 0.05$) but all pairwise comparisons versus the combination group are significant ($p \leq 0.05$) then the combination effect is declared *additive*. Otherwise, the combination effect is inconclusive (no effect).

It is important to note that the LS Means used for the combination analysis and reported output, were estimated from a RM ANOVA model consisting only the 5 groups related to each combination (*i.e.*, *control*, *single agent 1*, *single agent 2*, *single agent 3*, and the *triple*

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combination), and not by fitting each group separately as was done for the Tumor Growth Inhibition analysis. While the estimates are similar, they may not match exactly.

[866] Further Testing for Cross-Resistance in MDA453 Cells

[867] The purpose of these experiments was to determine whether MDA453 cells that had acquired resistance to the PI3K α specific inhibitor Compound 21 had cross-resistance to other PI3K α specific inhibitors in cell proliferation assays.

[868] MDA453 cells that are resistant to Compound 21 (Cpd 21-R) were created as described above and determined to have an M1043I second-site mutation. The Cpd 21-R cells then were tested for cross-resistance by performing a cell proliferation assay in the presence of increasing concentrations of PI3K α specific inhibitors Compound 21, alpelisib, and Compound HP1. The results are presented in Fig. 30. The cross-resistance cells demonstrated increased levels of resistance relative to naïve cells in varying degrees.

[869] Further Testing for Cross-Resistance in Engineered T47D cells

[870] The purpose of these experiments was to determine whether T47D cells that had been engineered to have 6 $\times$ M1043I second-site mutations were resistant to PI3K α specific inhibitors.

[871] T47D (6 $\times$ M1043I) cells were created as described above. The T47D (6 $\times$ M1043I) cells then were tested for cross-resistance by performing a cell proliferation assay in the presence of increasing concentrations of PI3K α specific inhibitors Compound 21, alpelisib, and Compound HP1. The results are presented in Fig. 31. The cross-resistance cells demonstrated increased levels of resistance relative to naïve cells in varying degrees.

[872] Treatment of Compound 21 resistant SUM185PE cells.

[873] The purpose of these experiments was to determine whether SUM185PE cells that had acquired resistance to the PI3K α specific inhibitor Compound 21 had cross-resistance to other PI3K α specific inhibitors in cell proliferation assays.

[874] SUM185PE cells that are resistant to Compound 21 (Cpd 21-R) were created as described

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above. The Cpd 21-R cells then were tested for cross-resistance by performing a cell proliferation assay in the presence of increasing concentrations of PIK3 α specific inhibitors Compound 1, Compound 21, alpelisib, and Compound HP1. The results are presented in Fig. 32. The cross-resistance cells demonstrated increased levels of resistance relative to naïve cells in varying degrees.

[875] Treatment of MDA453 naïve cells with combination of alpelisib and Compound 21.

[876] MDA453 naïve cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound 21 were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 33). A Combination Index was plotted versus Total Dose. (See Fig. 34).

[877] Treatment of MDA453 naïve cells with combination of Compound HP1 and Compound 21.

[878] MDA453 naïve cells were treated with increasing concentrations of Compound HP1 in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 35). A Combination Index was plotted versus Total Dose. (See Fig. 36).

[879] Treatment of MDA453 naïve cells with combination of alpelisib and Compound HP1.

[880] MDA453 naïve cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound HP1. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 37). A Combination Index was plotted versus Total Dose. (See Fig. 38).

[881] Treatment of SUM185PE (H1047R homozygous) cells with combination of alpelisib and Compound 21.

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[882] SUM185PE (H1047R homozygous) cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 39).

[883] Treatment of Cpd-21-R SUM185PE (H1047R homozygous) cells with combination of alpelisib and Compound 21.

[884] SUM185PE (H1047R homozygous) cells that were resistant to Compound 21 (Cpd-21-R) and generated as described above were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 40).

[885] Treatment of SUM185PE (H1047R homozygous) cells with combination of Compound HP1 and Compound 21.

[886] SUM185PE (H1047R homozygous) cells were treated with increasing concentrations of HP1 in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 41).

[887] Treatment of SUM185PE (H1047R homozygous) cells with combination of alpelisib and Compound HP1.

[888] SUM185PE (H1047R homozygous) cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound HP1. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 42).

[889] Treatment of T47D cells with combination of alpelisib and Compound 21.

[890] T47D cells were treated with increasing concentrations of alpelisib in combination with

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increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 43).

[891] Treatment of T47D cells with combination of Compound HP1 and Compound 21.

[892] T47D cells were treated with increasing concentrations of HP1 in combination with increasing concentrations of Compound 21. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 44).

[893] Treatment of T47D cells with combination of alpelisib and Compound HP1.

[894] T47D cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound HP1. An *in vitro* signaling assay for PI3K α substrates p-AKT and p-S6 was performed essentially as described above. (See Fig. 45). A cell proliferation assay also was performed essentially as described above and %Inhibition was plotted versus Dose (log/ μ M). (See Fig. 46). EC₅₀ values were calculated for alpelisib and Compound 21 either in single dose or in combination. (See Fig. 46).

[895] Treatment of Engineered T47D Cells (having 6 $\times$ M1043I 2nd site mutations) with combination of alpelisib and Compound HP1.

[896] Engineered T47D Cells (having 6 $\times$ M1043I 2nd site mutations) cells were treated with increasing concentrations of alpelisib in combination with increasing concentrations of Compound HP1. A cell proliferation assay was performed essentially as described above and %Inhibition was plotted versus Dose (log/ μ M). (See Fig. 47). EC₅₀ values were calculated for alpelisib and Compound 21 either in single dose or in combination. (See Fig. 47).

[897] Treatment of Parental SUM185PE cells or Compound 21 Resistant (Cpd-21-R) SUMPPE185 Cells.

[898] Parental SUM185PE cells or Compound 21 resistant (Cpd-21-R) SUM185PE cells were treated with increasing concentrations of Compound 21, alpelisib, Compound HP1, Compound HP4, Compound HP5, or Compound HP6. A cell proliferation assay was performed essentially

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as described above and %Inhibition was plotted versus Dose (log/ μ M). (See Fig. 48). EC₅₀ values were calculated for parental SUM185PE cells and Cpd-21-R SUM185PE for each compound and fold-change was calculated as indicated in Table R.

[899] Table R. EC₅₀ of Selected Compounds in Compound 21-Resistant SUM185PE Cells

	Alpelisib	Compound 21	Compound HP1	Compound HP4	Compound HP5	Compound HP6
Parental	311	2.4	53	67	33	36
Cpd 21-R	723	211	78	117	43	45
Fold-Change	2.3×	88×	1.5×	1.7×	1.3×	1.2×

[900] Treatment of T47D Cells or T47D Cells Having 2nd Site Mutations.

[901] T47D cells (5×H1047R/1×WT) or T47D cells that were engineered to have 2nd site mutations (5×H1047R/6×C901F) or (6×H1047R/M1043I) were treated with increasing concentrations of Compound 21, alpelisib, Compound HP1, Compound HP4, Compound HP5, or Compound HP6. A cell proliferation assay was performed essentially as described above and %Inhibition was plotted versus Dose (log/ μ M). (See Fig. 49). EC₅₀ values were calculated for T47D cells, T47D (5×H1047R/6×C901F) cells, and T47D (6×H1047R/M1043I) cells for each compound as indicated in Table S.

[902] Table S. EC₅₀ of Selected Compounds in T47D cells, T47D (5×H1047R/6×C901F) cells, and T47D (6×H1047R/M1043I) cells

	Alpelisib	Compound 21	Compound HP1	Compound HP4	Compound HP5	Compound HP6
T47D	109	1.1	16	17	6.0	6.1
(5×H1047R/6×C901F)	89	153	9.0	10.3	3.8	2.6
(6×H1047R/M1043I)	299	126	40	53	17	19

[903] Treatment of T47D Cells with Combination of Compound 21 and Compound HP6

[904] T47D cells were treated with increasing concentrations of Compound 21 in combination

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with increasing concentrations of Compound HP6. An *in vitro* signaling assay for PI3K α substrates p-AKT and FOXM1 was performed essentially as described above. (See Fig. 50). A cell proliferation assay was performed essentially as described above and % Growth Inhibition was plotted versus Dose of Compound 21 (log/ μ M). (See Fig. 51). EC₅₀ values and EC₉₀ values for Compound 21 in the presence of Compound HP6 were calculated as indicated in Table T. A Combination Index was plotted versus Growth Inhibition. (See Fig. 52).

[905] Table T. EC₅₀ values and EC₉₀ values for Compound 21 in the presence of Compound HP6 in T47D Cells.

	<u>EC₅₀ (nM)</u>	<u>Fold-Change</u>	<u>EC₉₀ (nM)</u>	<u>Fold-Change</u>
Compound 21	1.3	-	4.4	-
Compound 21 + Compound HP6 (3.1 nM)	0.9	1.4×	3.8	1.1×
Compound 21 + Compound HP6 (6.2 nM)	0.7	1.9×	3.4	1.3×
Compound 21 + Compound HP6 (12.5 nM)	0.4	3.2×	2.1	2.1×
Compound 21 + Compound HP6 (25 nM)	0.08	16×	1.6	2.7×

[906] Treatment of SUMPE Cells with Combination of Compound 21 and Compound HP6

[907] SUMPE cells were treated with increasing concentrations of Compound 21 in combination with increasing concentrations of Compound HP6. A cell proliferation assay was performed essentially as described above and % Growth Inhibition was plotted versus Dose of Compound 21 (log/ μ M). (See Fig. 53). EC₅₀ values and EC₉₀ values for Compound 21 in the presence of Compound HP6 were calculated as indicated in Table U. A Combination Index was plotted versus Growth Inhibition. (See Fig. 54).

[908] Table U. EC₅₀ values and EC₉₀ values for Compound 21 in the presence of Compound

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HP6 in SUMPE Cells.

	<u>EC₅₀ (nM)</u>	<u>Fold-Change</u>	<u>EC₉₀ (nM)</u>	<u>Fold-Change</u>
Compound 21	1.2	-	5.9	-
Compound 21 + Compound HP6 (7.8 nM)	0.77	1.5×	3.7	1.6×
Compound 21 + Compound HP6 (15.6 nM)	0.45	2.7×	3.5	1.7×
Compound 21 + Compound HP6 (31.2 nM)	0.15	8×	2.0	2.9×

[909] Treatment of T47D Cells with Combination of Compound 21 and Compound HP5

[910] T47D cells were treated with increasing concentrations of Compound 21 in combination with increasing concentrations of Compound HP5. A cell proliferation assay was performed essentially as described above and % Growth Inhibition was plotted versus Dose of Compound 21 (log/ μ M). (See Fig. 55). A Combination Index was plotted versus Growth Inhibition. (See Fig. 56).

[911] Treatment of SUMPE Cells with Combination of Compound 21 and Compound HP5

[912] SUMPE cells were treated with increasing concentrations of Compound 21 in combination with increasing concentrations of Compound HP5. A cell proliferation assay was performed essentially as described above and % Growth Inhibition was plotted versus Dose of Compound 21 (log/ μ M). (See Fig. 57). A Combination Index was plotted versus Growth Inhibition. (See Fig. 58).

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SEQUENCE LISTING

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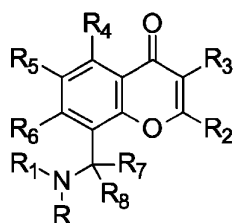
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1021 yirktlaldk teqealeyfm kqmdahhgg wttkmdwifh tikqhaln

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CLAIMS

1. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, the method comprising administering to the patient:

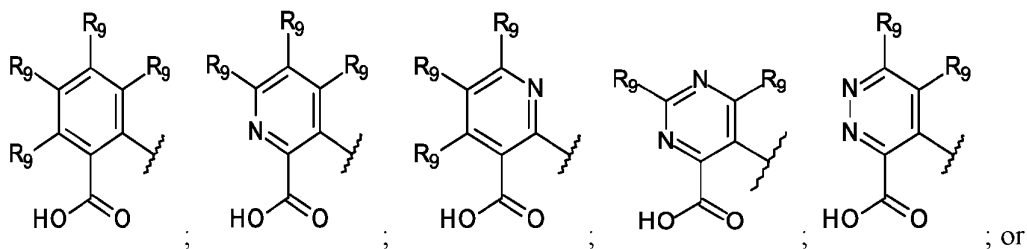
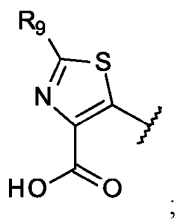
- (i) a therapeutically effective amount of a first PI3K α selective inhibitor of a formula:



or pharmaceutically acceptable salt thereof, wherein:

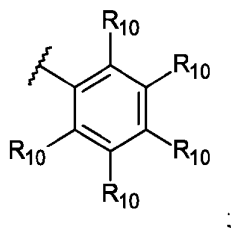
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:

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R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl; and

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- (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor is a PI3K α selective orthosteric inhibitor, selected from alpelisib, inavolisib, or a pharmaceutically acceptable salt thereof;

wherein the therapeutically effective amount of the first PI3K α selective inhibitor and the therapeutically effective amount of the second PI3K α selective inhibitor are administered simultaneously, separately, or sequentially.

2. The method of claim 1, wherein the second PI3K α selective inhibitor is alpelisib or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or claim 2, wherein the second PI3K α selective inhibitor is inavolisib or a pharmaceutically acceptable salt thereof.

4. The method of any of claims 1-3, the dose of the second PI3K α selective inhibitor is less than about a 300 mg oral dose administered every day.

5. The method of claim 4, wherein the first PI3K α selective inhibitor and the second PI3K α selective inhibitor are administered substantially simultaneously.

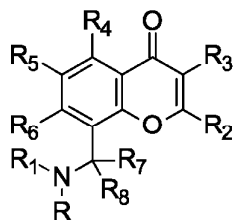
6. The method of any of claims 1-5, wherein the dose of the second PI3K α selective inhibitor is less than about a 50, 30, 12.5, 6.25, or 3.125 mg/kg oral dose administered every day.

7. The method of claim 6, wherein the first PI3K α selective inhibitor and the second PI3K α selective inhibitor are administered substantially simultaneously.

8. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, the method comprising administering to the patient:

- (i) a therapeutically effective amount of a first PI3K α selective inhibitor that binds to PI3K α allosteric pocket 1 and is of a formula:

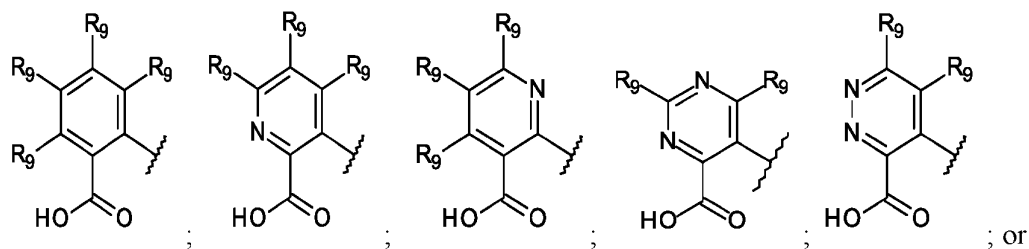
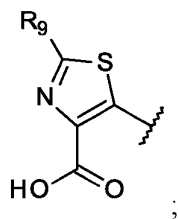
- 444 -



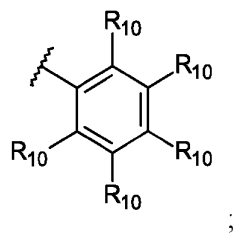
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected

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from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

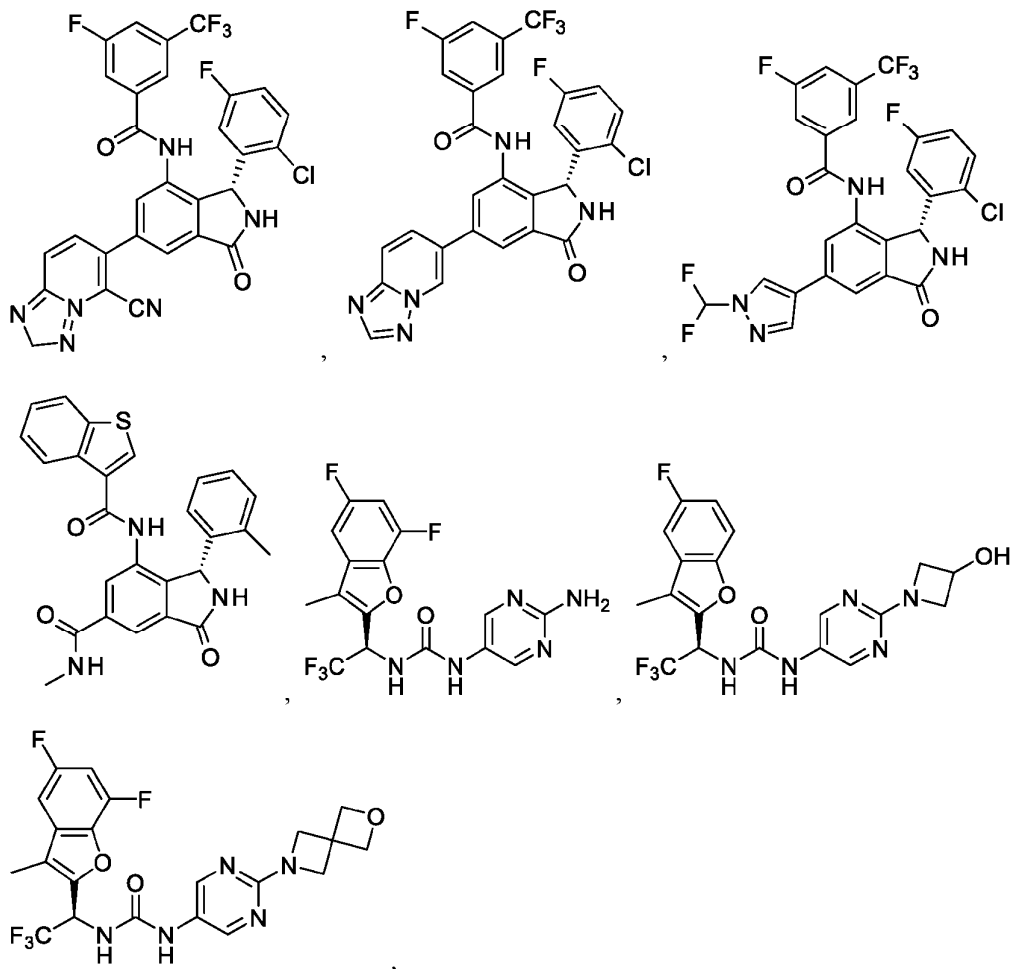
R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl; and

- (ii) a therapeutically effective amount of a second PI3K α selective inhibitor, wherein the second PI3K α selective inhibitor is selected from:

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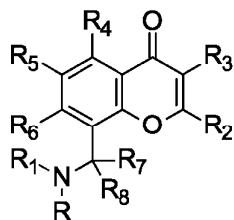
and pharmaceutically acceptable salts thereof;

wherein the first PI3K α selective inhibitor and the second PI3K α selective inhibitor are administered simultaneously, separately, or sequentially.

9. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, the method comprising administering to the patient:

- (i) a therapeutically effective amount of a first PI3K α selective inhibitor of a formula:

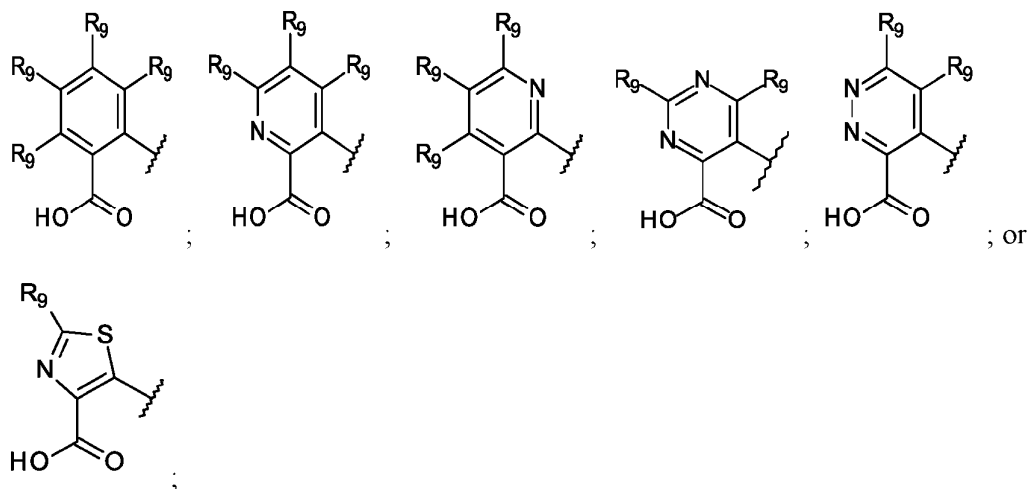
- 447 -



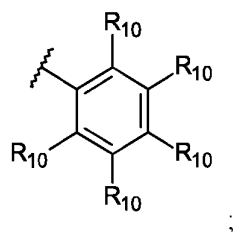
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected

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from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

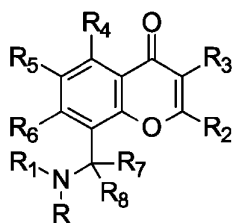
R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each **R₁₁** is independently -H or C₁-C₃ alkyl; and

- (ii) a therapeutically effective amount of a second PI3K α selective inhibitor of a formula:

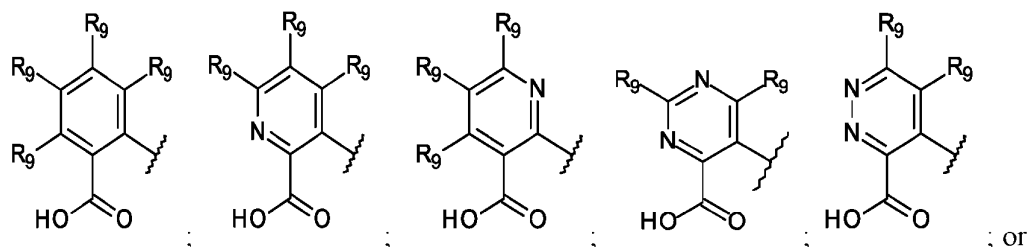
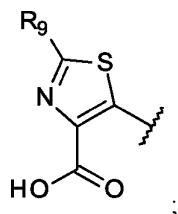


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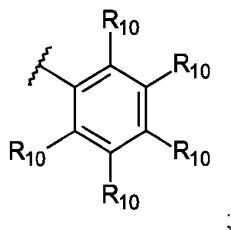
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of **R**₄, **R**₅ and **R**₆ is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

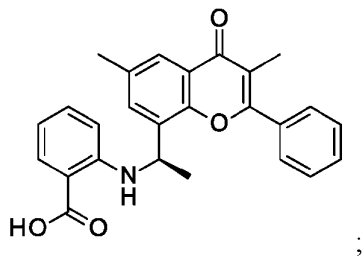
R₈ is -H or C₁-C₆ alkyl;

each **R**₉ is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R**₁₀ is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆

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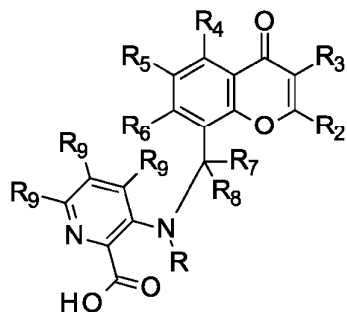
haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, an optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, an optionally substituted $\text{C}_2\text{-C}_6$ alkynyl, an optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, or $\text{C}_2\text{-C}_6$ alkynyl is each optionally substituted with a $-\text{CN}$, $-\text{OH}$, oxetanyl, or $\text{C}_1\text{-C}_3$ alkoxy; the optionally substituted $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{OH}$ or $-\text{CN}$; and each R_{11} is independently $-\text{H}$ or $\text{C}_1\text{-C}_3$ alkyl, provided that the second $\text{PI3K}\alpha$ selective inhibitor is not a compound of a formula:



wherein the first $\text{PI3K}\alpha$ selective inhibitor and the second $\text{PI3K}\alpha$ selective inhibitor are different and are administered simultaneously, separately, or sequentially.

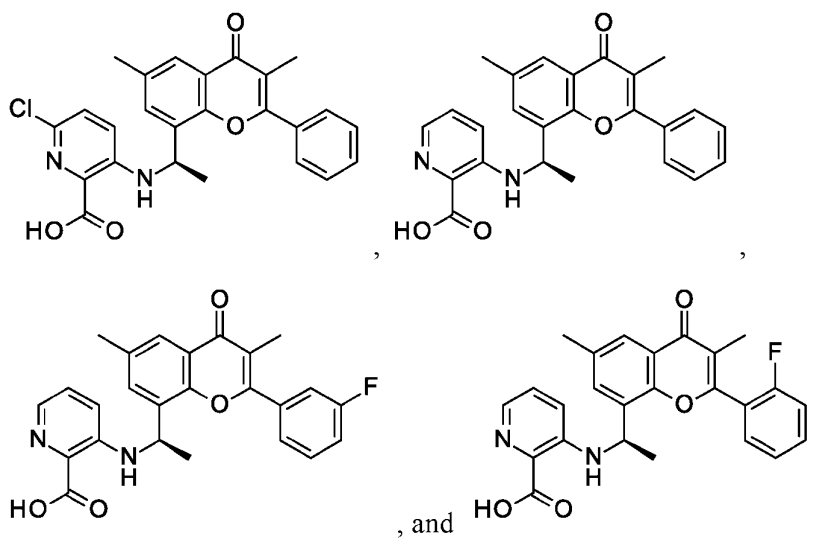
10. The method of claim 9, wherein the second $\text{PI3K}\alpha$ selective inhibitor is of a formula:

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or a pharmaceutically acceptable salt thereof.

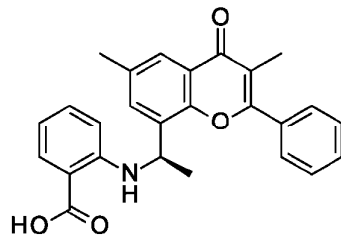
11. The method of claim 9 or 10, wherein the second PI3K α selective inhibitor is of a formula selected from:



or a pharmaceutically acceptable salt thereof.

12. The method of any of claims 1-11, wherein the first PI3K α selective inhibitor is of a formula:

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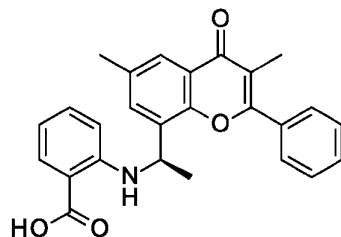


or a pharmaceutically acceptable salt thereof.

13. The method of any of claims 1-12, wherein the therapeutically effective amount of the first PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

14. The method of any of claims 1-13, wherein the therapeutically effective amount of the second PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

15. The method of any of claims 1-14, wherein the first PI3K α selective inhibitor is of a formula:



or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein the therapeutically effective amount of the first PI3K α selective inhibitor administered to the patient is a 100-1200 mg oral dose administered two times daily.

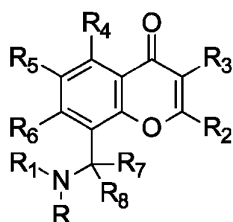
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17. The method of claim 15, wherein the therapeutically effective amount of the first PI3K α specific inhibitor administered to the patient is a 9-75 mg/kg oral dose administered two times daily.

18. The method of any of claims 1-17, wherein the method comprises administering the second PI3K α specific inhibitor after the disease or disorder has developed resistance to the first PI3K α specific inhibitor.

19. The method of claim 18, wherein the resistance is characterized by occurrence of an M1043I/L mutation or a C901F mutation.

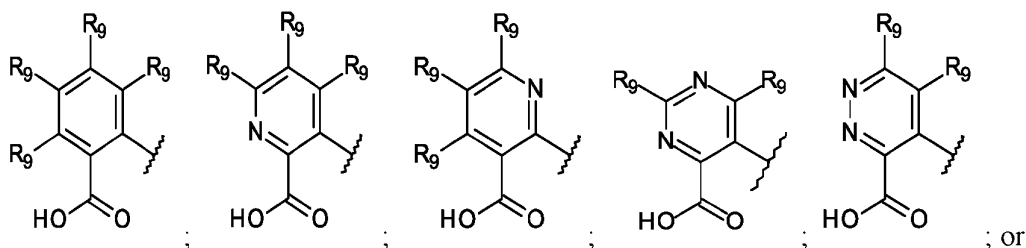
20. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) that is resistant to treatment with alpelisib, the method comprising administering to a patient in need thereof a therapeutically effective amount of a PI3K α selective inhibitor of a formula:



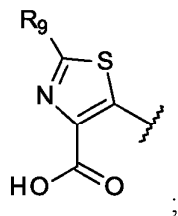
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

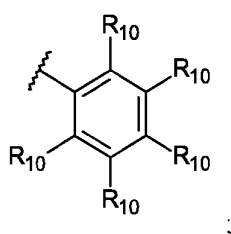
R₁ is a group of the formula:



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R_2 is a group of the formula:



R_3 is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of R_4 , R_5 and R_6 is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R_7 is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

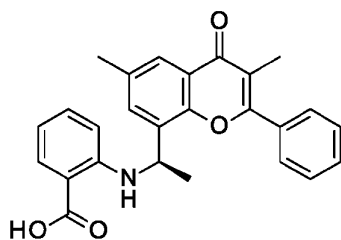
R_8 is -H or C₁-C₆ alkyl;

each R_9 is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

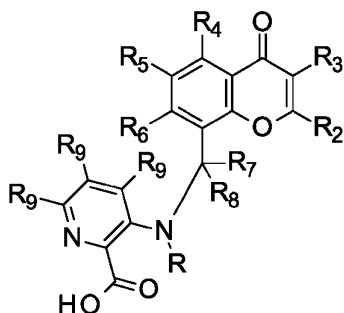
each R_{10} is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-\text{SO}_2\text{R}_{11}$, $-\text{CONR}_{11}\text{R}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{NR}_{11}-\text{CO}_2\text{R}_{11}$, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally

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substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and each R₁₁ is independently -H or C₁-C₃ alkyl, provided that the PI3K α selective inhibitor that is administered in the method is not a compound of a formula:



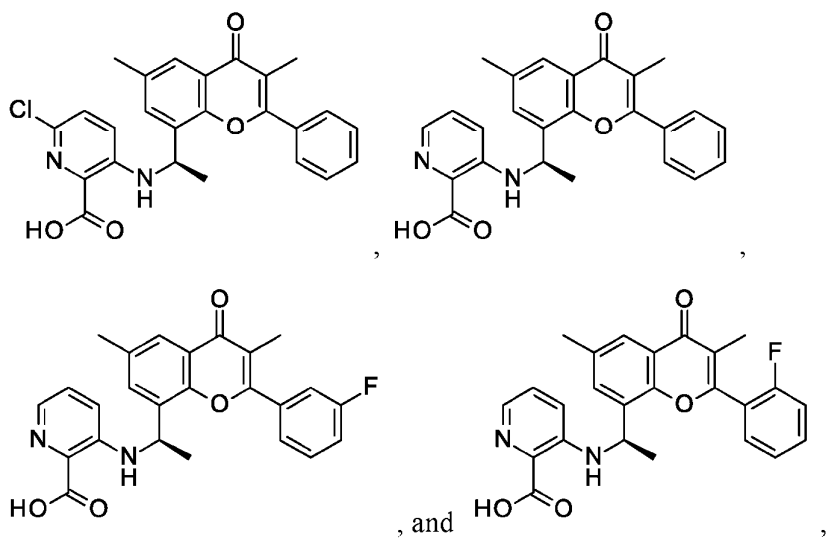
21. The method of claim 20, wherein the PI3K α selective inhibitor is of a formula:



or a pharmaceutically acceptable salt thereof.

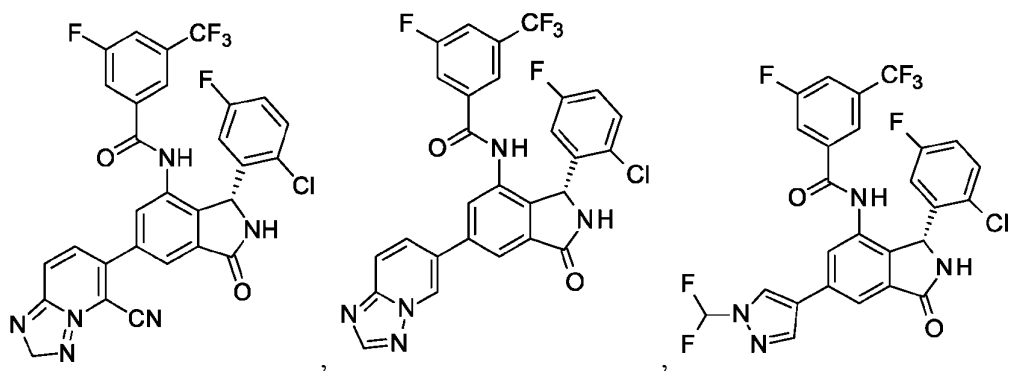
22. The method of claim 20 or 21, wherein the second PI3K α selective inhibitor is of a formula selected from:

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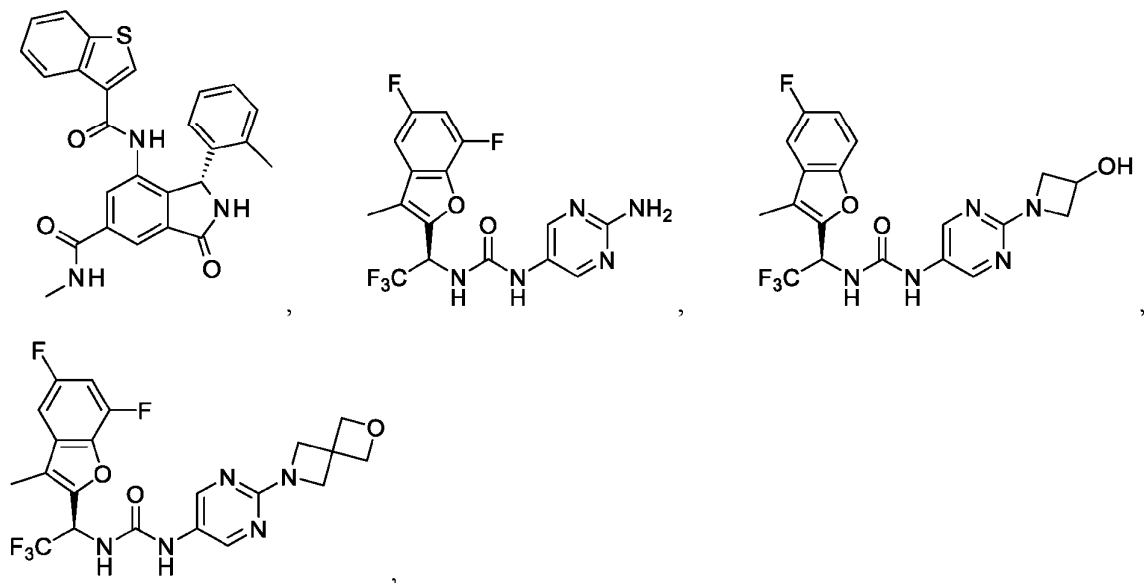


or a pharmaceutically acceptable salt thereof.

23. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha ($\text{PI3K}\alpha$) that is resistant to treatment with alpelisib, the method comprising administering to a patient in need thereof a therapeutically effective amount of a $\text{PI3K}\alpha$ selective inhibitor that binds to $\text{PI3K}\alpha$ allosteric pocket 2 selected from:

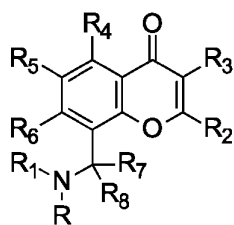


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and pharmaceutically acceptable salts thereof.

24. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient has been treated previously with a therapeutically effective amount of a first PI3K α selective inhibitor of a formula:

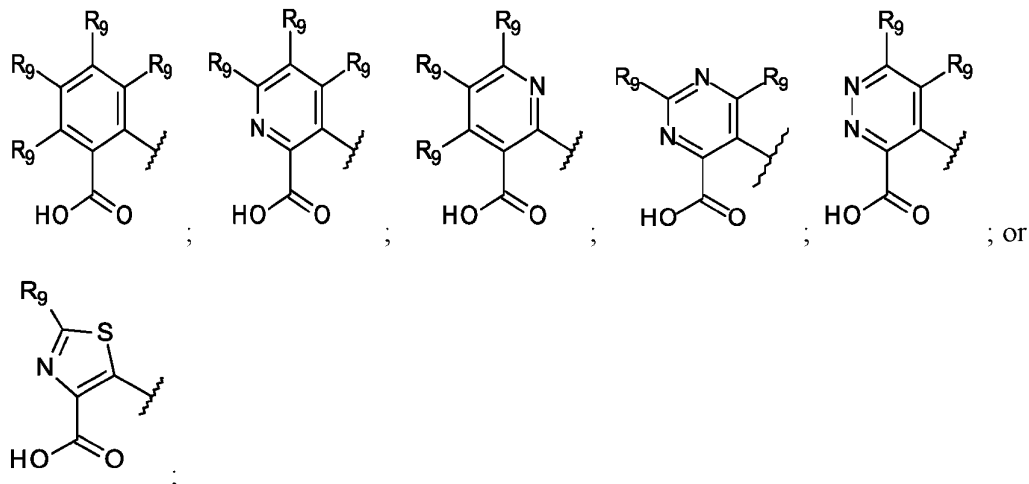


or pharmaceutically acceptable salt thereof, wherein:

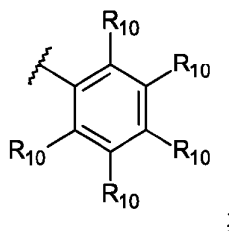
R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:

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R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from

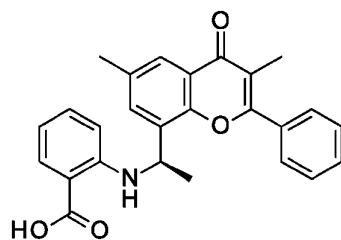
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pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

each R₁₁ is independently -H or C₁-C₃ alkyl;

and the patient has a cancer which has acquired an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, the method comprising administering to the patient a therapeutically effective amount of a second PI3K α selective inhibitor selected from alpelisib, inavolisib, or a pharmaceutically acceptable salt thereof.

25. The method of claim 24, wherein the first PI3K α selective inhibitor is of a formula:

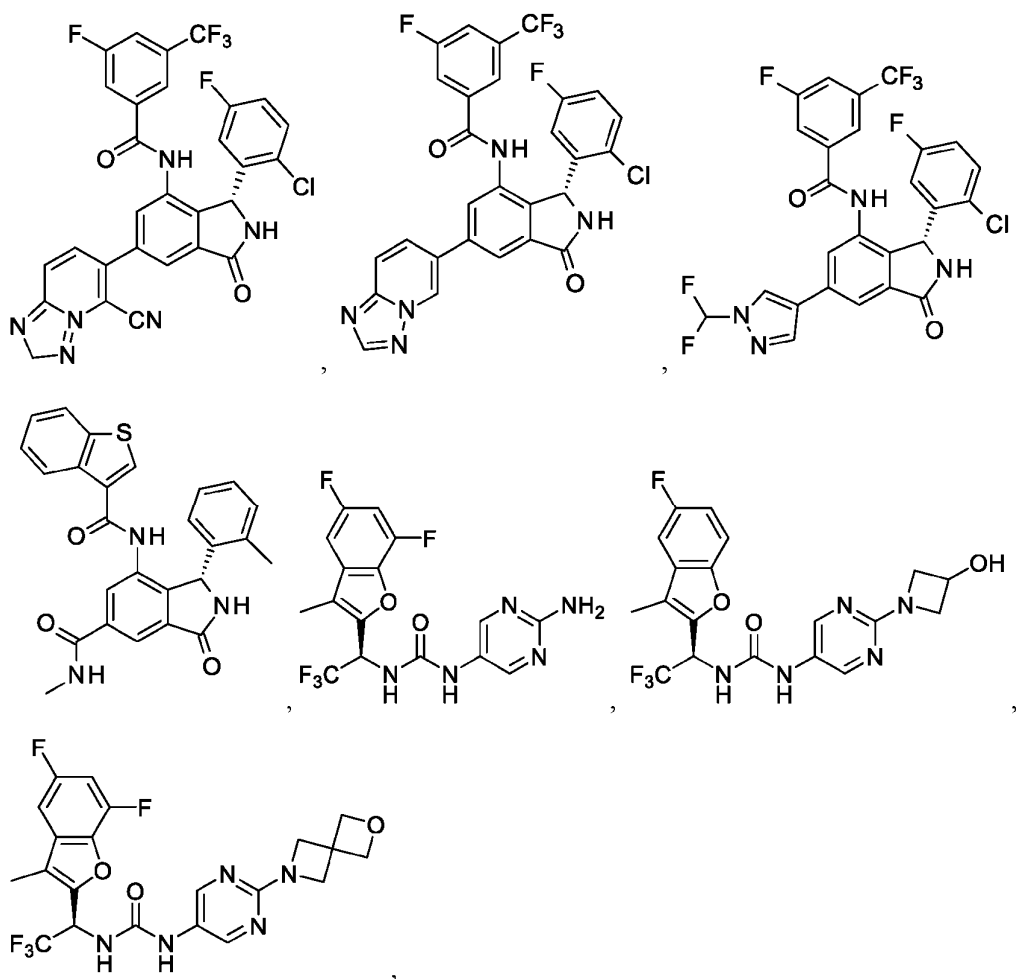


or a pharmaceutically acceptable salt thereof.

26. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, the method comprising administering to the patient a

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therapeutically effective amount of a PI3K α selective inhibitor that binds to PI3K α allosteric pocket 2 selected from:

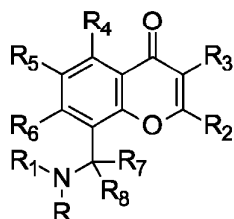


and pharmaceutically acceptable salts thereof.

27. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F

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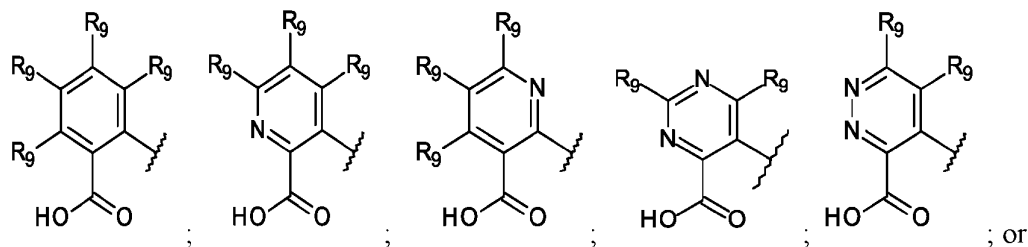
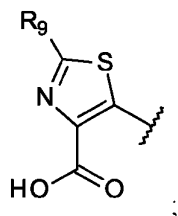
mutation in *cis* with an H1047R mutation, the method comprising administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor of a formula:



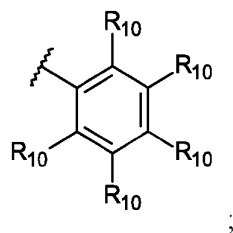
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or a heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected

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from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

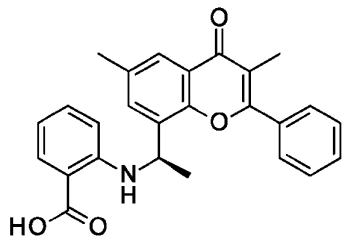
R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

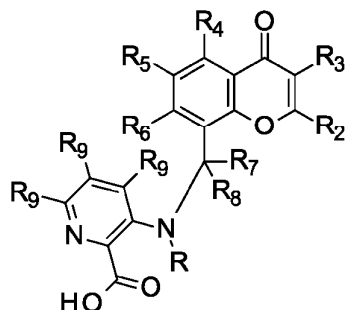
each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

each **R₁₁** is independently -H or C₁-C₃ alkyl, provided that the PI3K α selective inhibitor that is administered in the method is not a compound of a formula:



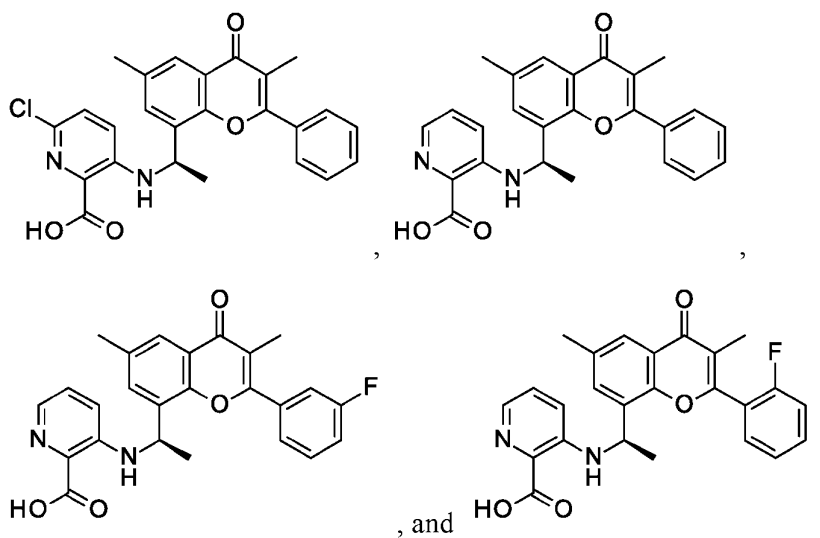
28. The method of claim 27, wherein the PI3K α selective inhibitor is of a formula:

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or a pharmaceutically acceptable salt thereof.

29. The method of claim 27 or 28, wherein the PI3K α selective inhibitor is selected from:



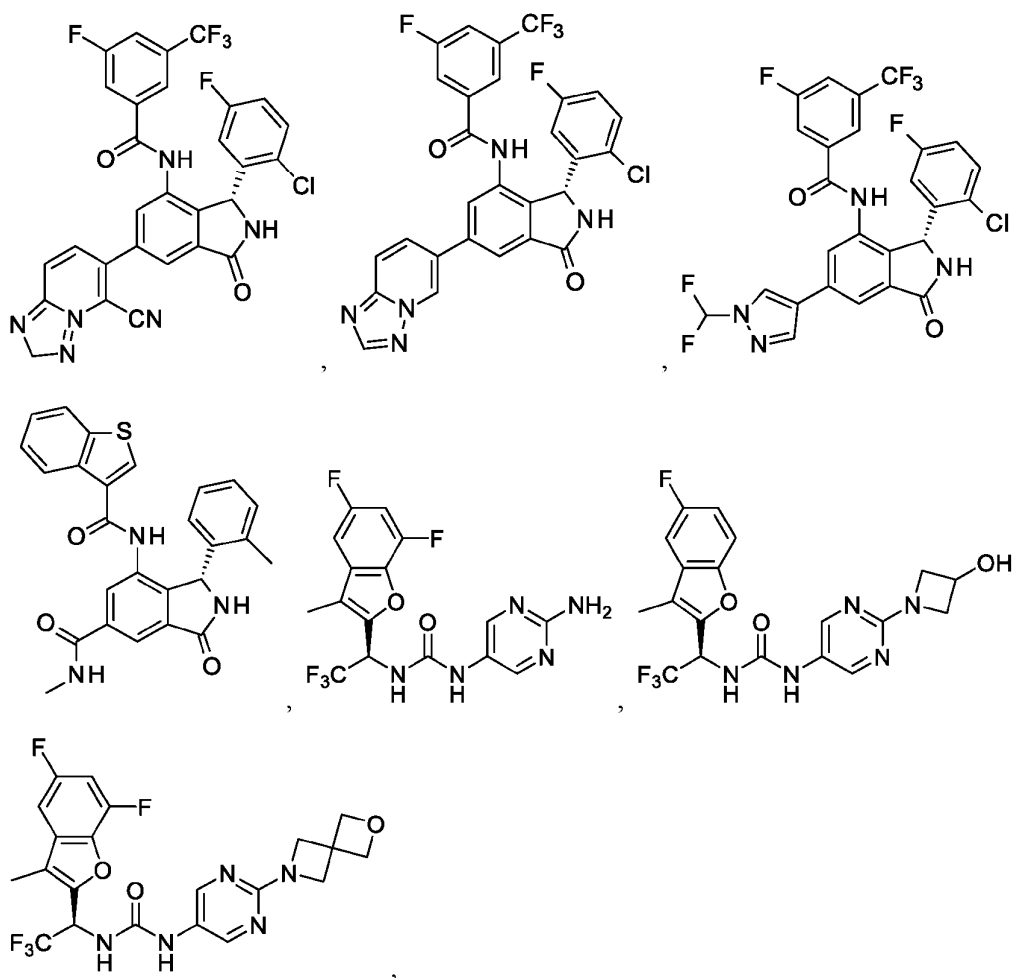
or a pharmaceutically acceptable salt thereof

30. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, the method comprising: determining that the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, and administering to the

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patient a therapeutically effective amount of a PI3K α selective inhibitor selected from alpelisib and inavolisib.

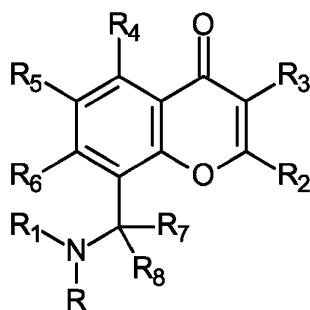
31. A method for treating a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, the method comprising: determining that the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, and administering to the patient a therapeutically effective amount of a PI3K α selective inhibitor, wherein the PI3K α selective inhibitor binds to PI3K α allosteric pocket 2 selected from.



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and pharmaceutically acceptable salts thereof.

32. A method of selecting a patient having a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) for treatment with a therapeutically effective amount of a PI3K α specific inhibitor compound of formula:

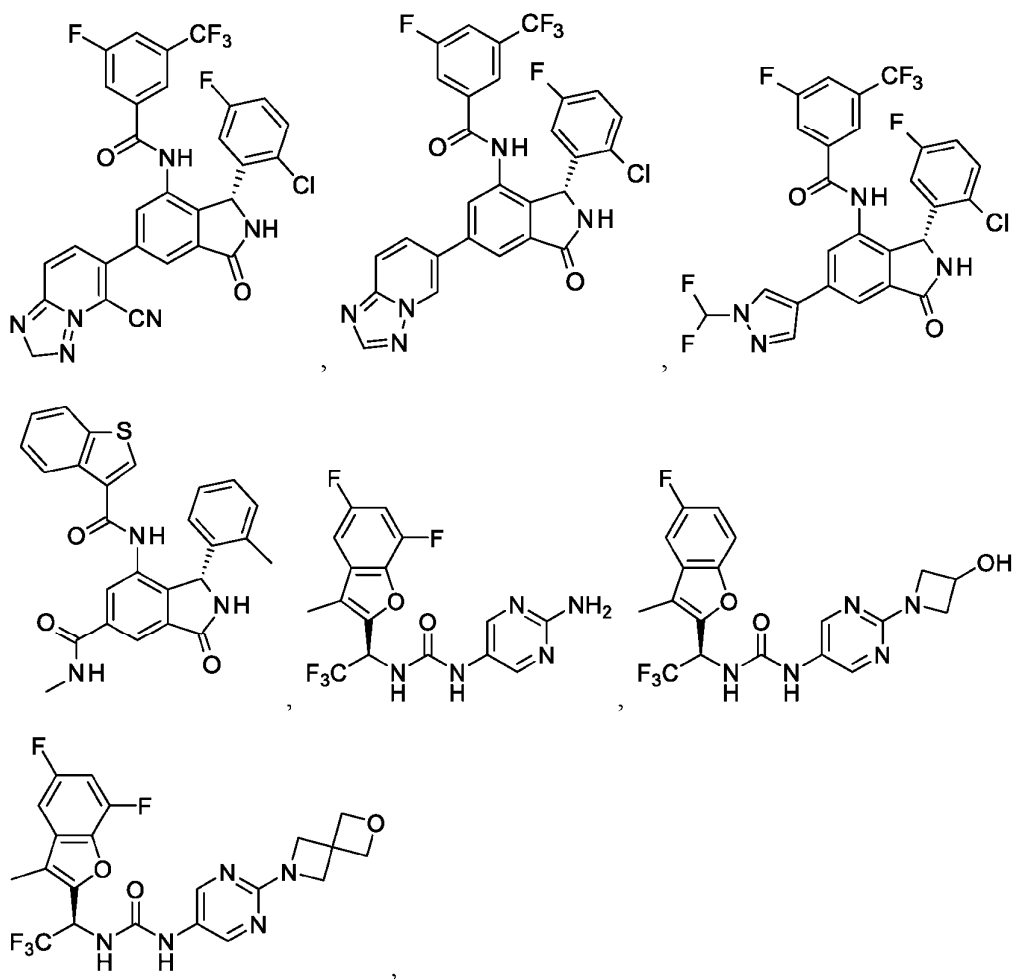


or a pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 1, comprising assaying a sample from a patient, wherein the patient is selected if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present in the sample.

33. A method of selecting a patient having a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) for treatment with a therapeutically effective amount of a PI3K α specific inhibitor selected from alpelisib and inavolisib, comprising assaying a sample from a patient, wherein the patient is selected if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present in the sample.

34. A method of selecting a patient having a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) for treatment with a therapeutically effective amount of a PI3K α specific inhibitor that binds to PI3K α allosteric pocket 2 selected from:

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and pharmaceutically acceptable salts thereof;

wherein the patient is selected if an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present in the sample.

35. The method of any of claims 1-34, wherein the disease or disorder is cancer.

36. The method of any of claims 1-34, wherein the disease or disorder is breast cancer.

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37. The method of any of claims 1-34, wherein the disease or disorder is PIK3CA-mutated, advanced, or metastatic breast cancer.

38. The method of any of claims 1-34, wherein the disease or disorder is PIK3CA H1047R-mutant advanced, or metastatic breast cancer.

39. The method according to claim 38, wherein the PIK3CA H1047R-mutant advanced, or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

40. The method of any of claims 1-39, wherein the patient is a postmenopausal female.

41. The method of any of claims 1-39, wherein the patient has type II diabetes mellitus.

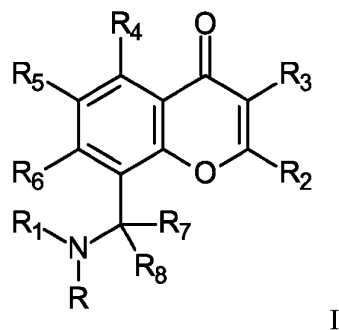
42. The method of any of claims 1-39, further comprising administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

43. The method according to claim 42, wherein the SERD is selected from imlunestrant, fulvestrant, giredestrant, amcenenestrant, rintodestrant, elacestrant, camizestrant, LSZ102, Zn-c5, and D-0502.

44. The method according to claim 42 or 43, wherein the therapeutically effective amount of the SERD is a 500 mg dose administered on days 1, 15, and 29.

45. A PI3K α specific inhibitor compound of Formula:

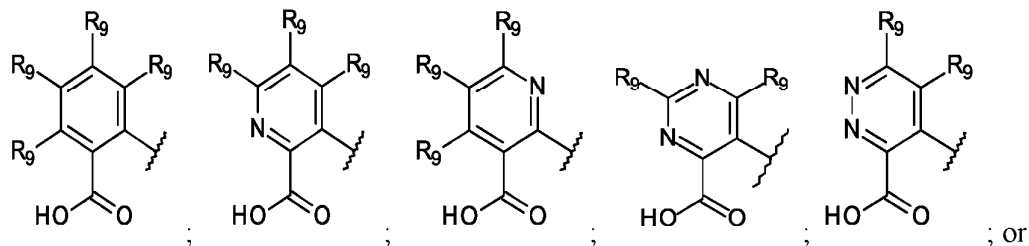
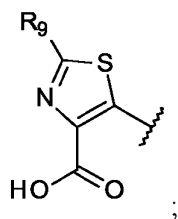
- 468 -



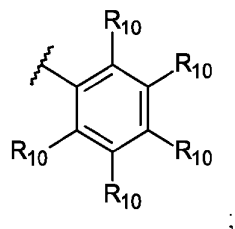
or a pharmaceutically acceptable salt thereof, wherein:

R is -H or C₁-C₃ alkyl;

R₁ is a group of the formula:



R₂ is a group of the formula:



R₃ is -H, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₅ cycloalkyl, a heterocycle of 3 to 5 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S, or

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a_heteroaryl of 5 or 6 ring atoms containing 1, 2, or 3 ring heteroatoms independently selected from N, O, or S;

each of **R₄**, **R₅** and **R₆** is independently -H, halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₇ is -CN, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R₈ is -H or C₁-C₆ alkyl;

each **R₉** is independently -H, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₃-C₅ cycloalkyl;

each **R₁₀** is independently -H, -CN, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -SO₂R₁₁, -CONR₁₁R₁₁, -NR₁₁R₁₁, -NR₁₁-CO₂R₁₁, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₃-C₅ cycloalkyl, an optionally substituted heterocycle selected from pyrrolidine, pyrrolidinone, piperidine or morpholine, an optionally substituted phenyl, an optionally substituted 1,3-benzodioxole, an optionally substituted 2,3-dihydro-1,4-benzodioxine, or an optionally substituted heteroaryl selected from pyrazole, isoxazole, isothiazole, imidazole, oxazole, or thiazole; wherein the optionally substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C₁-C₃ alkoxy; the optionally substituted C₃-C₅ cycloalkyl, phenyl, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, -SO₂R₁₁, -NR₁₁R₁₁, -OH or -CN; and

each **R₁₁** is independently -H or C₁-C₃ alkyl;

for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor which is a PI3K α specific orthosteric inhibitor selected from alpelisib, inavolisib, or a pharmaceutically acceptable salt thereof.

46. A compound for use according to claim 45, wherein the second PI3K α specific inhibitor is alpelisib or a pharmaceutically acceptable salt thereof.

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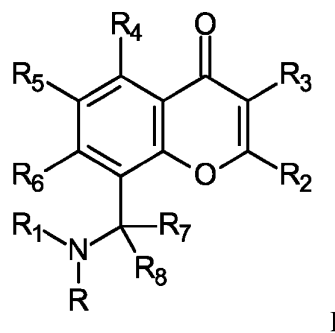
47. A compound for use according to claim 45, wherein the second PI3K α specific inhibitor is inavolisib or a pharmaceutically acceptable salt thereof.

48. A compound for use according to any of claims 45-47, wherein the dose of the second PI3K α specific inhibitor is less than about a 300 mg oral dose administered every day.

49. A compound for use according to any of claims 45-48, wherein the first PI3K α specific inhibitor and the second PI3K α specific inhibitor are administered substantially simultaneously.

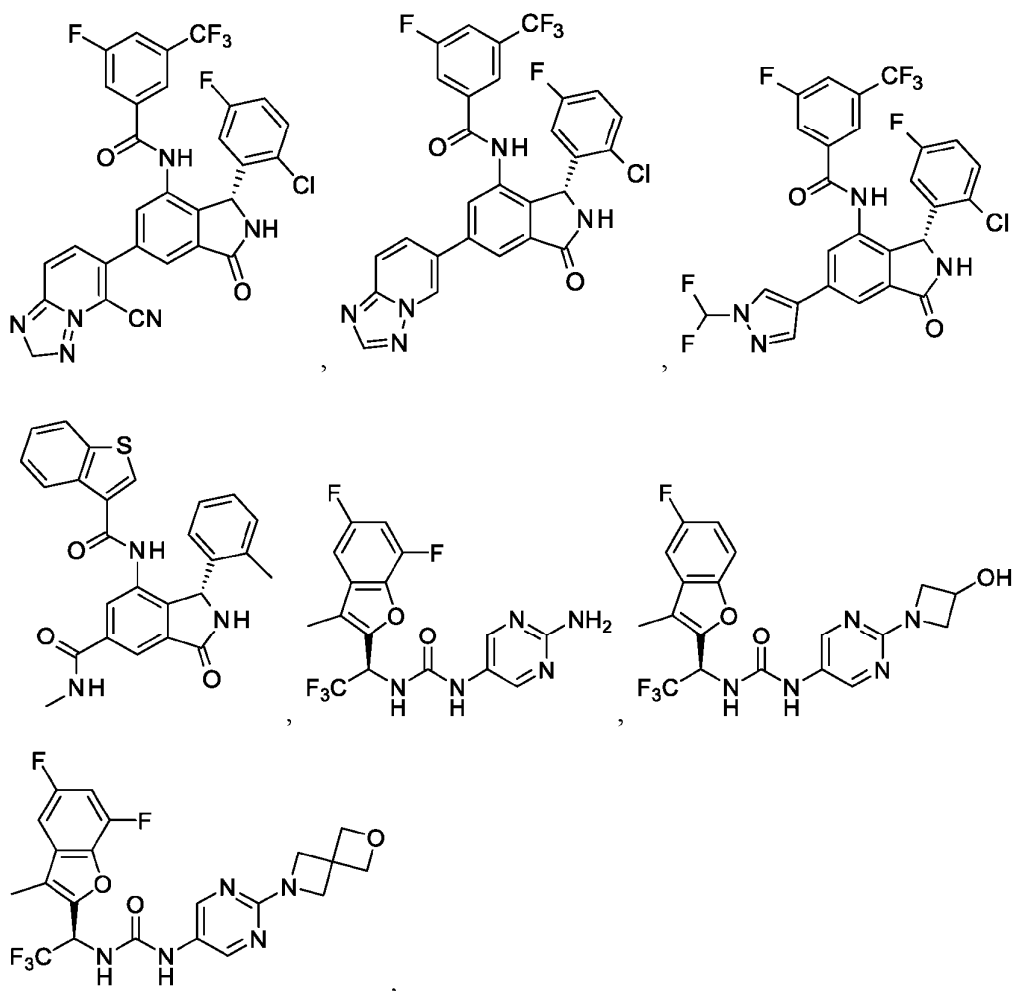
50. A compound for use according to any of claims 45-49, wherein the first PI3K α specific inhibitor and the second PI3K α specific inhibitor are administered simultaneously and the dose of the second PI3K α specific inhibitor is less than about a 50, 30, 12.5, 6.25, or 3.125 mg/kg oral dose administered every day.

51. A PI3K α specific inhibitor compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor which binds to PI3K α allosteric pocket 2 selected from

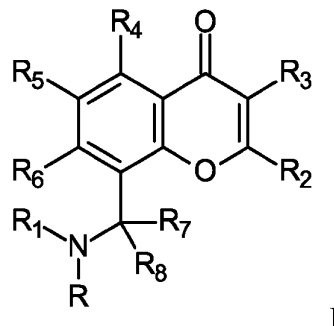
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and pharmaceutically acceptable salts thereof.

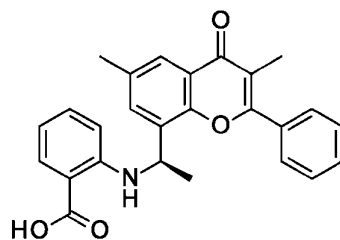
52. A PI3K α specific inhibitor compound of Formula I:

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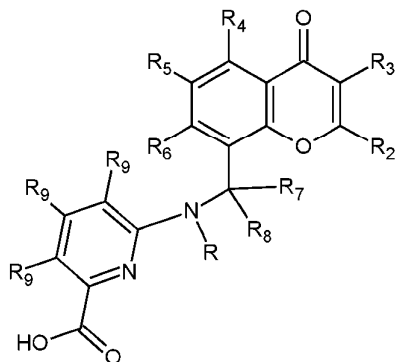
or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in simultaneous, separate or sequential combination with a second PI3K α specific inhibitor of Formula I or pharmaceutically acceptable salt thereof, wherein the first PI3K α specific inhibitor and the second PI3K α specific inhibitor are different.

53. A compound for use according to claim 52, wherein the second PI3K α specific inhibitor is not of a formula:



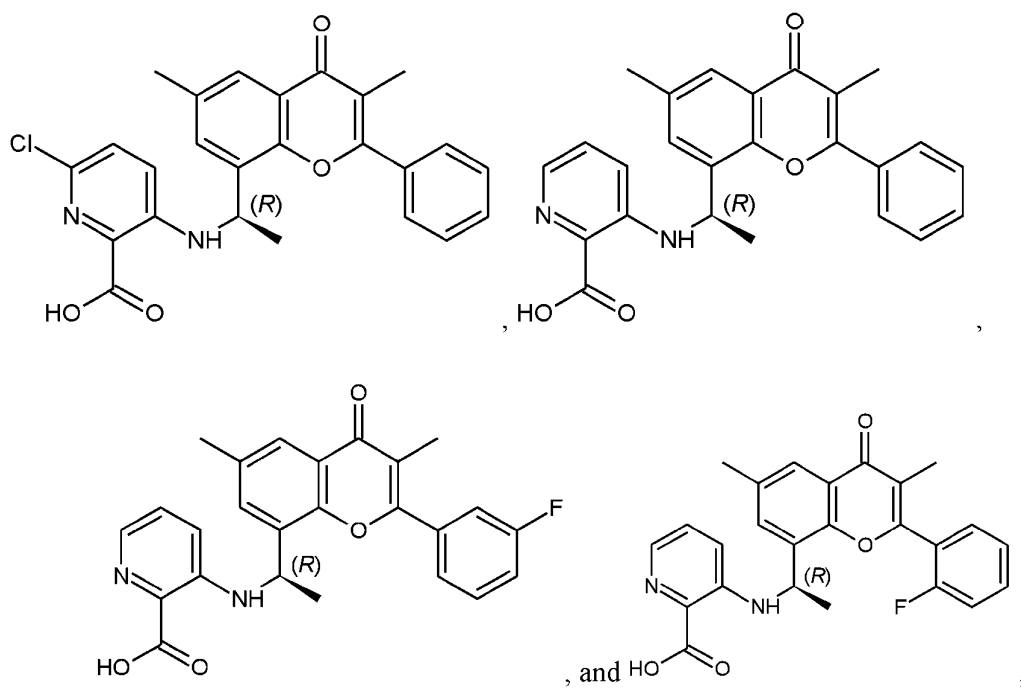
54. A compound for use according to claim 52 or 53, wherein the second PI3K α specific inhibitor is of a formula:

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or a pharmaceutically acceptable salt thereof.

55. A compound for use according to any of claims 52-54, wherein the second PI3K α specific inhibitor is of a formula selected from:



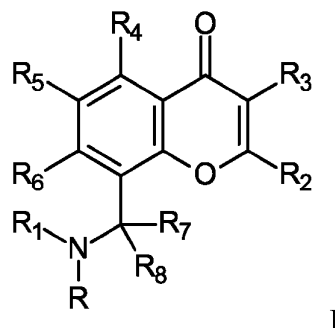
or a pharmaceutically acceptable salt thereof.

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56. A compound for use according to any of claims 52-55, wherein the therapeutically effective amount of the first PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

57. A compound for use according to any of claims 52-56, wherein the therapeutically effective amount of the second PI3K α specific inhibitor is effective for reducing PI3K α activity in the patient without inducing hyperglycemia in the patient.

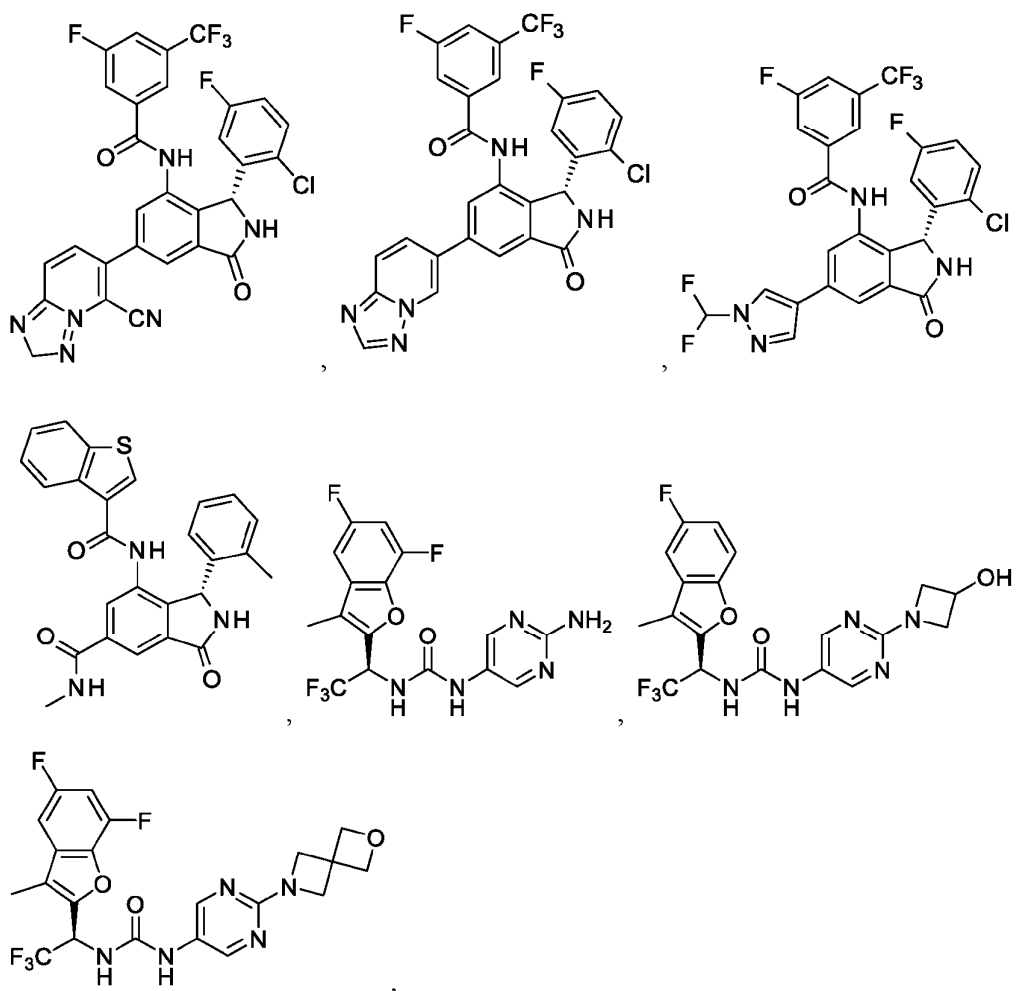
58. A PI3K α specific inhibitor compound of a Formula I:



or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45; for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), of a patient that is resistant to treatment with alpelisib or inavolisib.

59. A PI3K α specific inhibitor which binds to PI3K α allosteric pocket 2 selected from

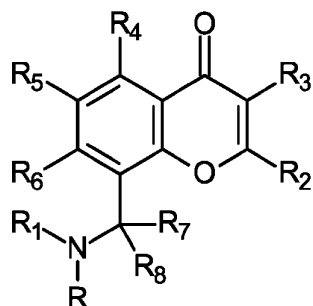
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and pharmaceutically acceptable salts thereof, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), of a patient having a cancer that is resistant to treatment with alpelisib or inavolisib.

60. A PI3K α specific inhibitor which is a PI3K α specific orthosteric inhibitor selected from alpelisib or inavolisib for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α), wherein the patient has been treated previously with compound of Formula I

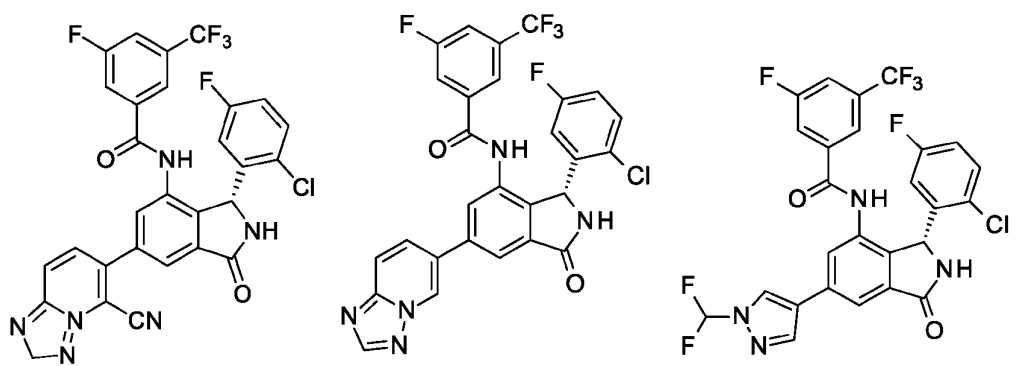
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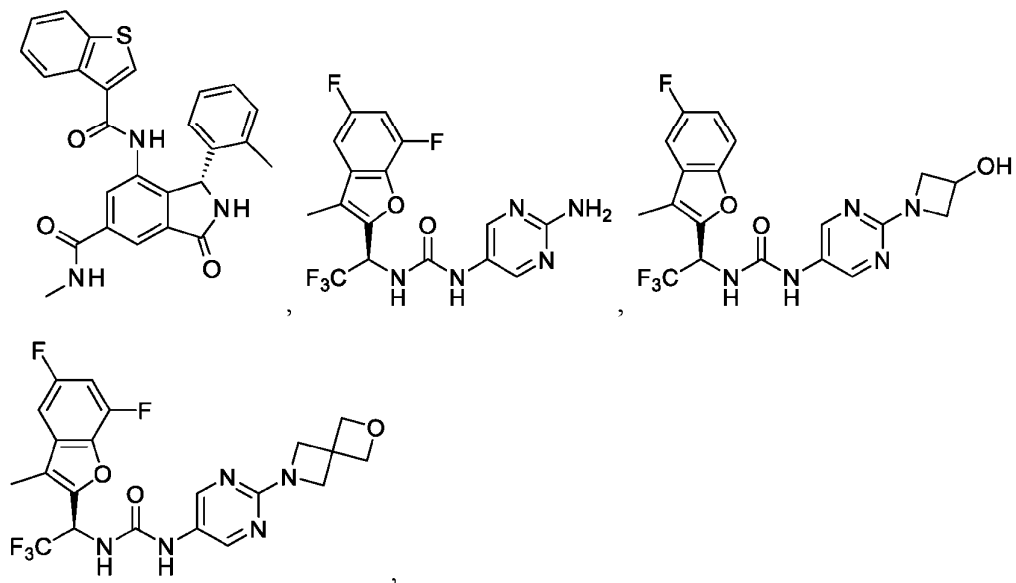
I

or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45, and the patient has a cancer which has acquired an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

61. A PI3K α specific inhibitor that binds to PI3K α allosteric pocket 2 selected from

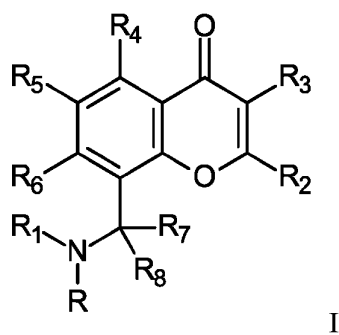


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and pharmaceutically acceptable salts thereof, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

62. A PI3K α specific inhibitor compound of Formula I:

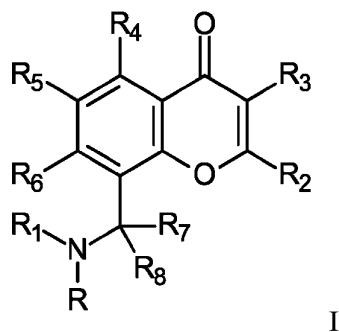


or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, wherein the patient

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has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation.

63. A PI3K α specific inhibitor compound of Formula I:

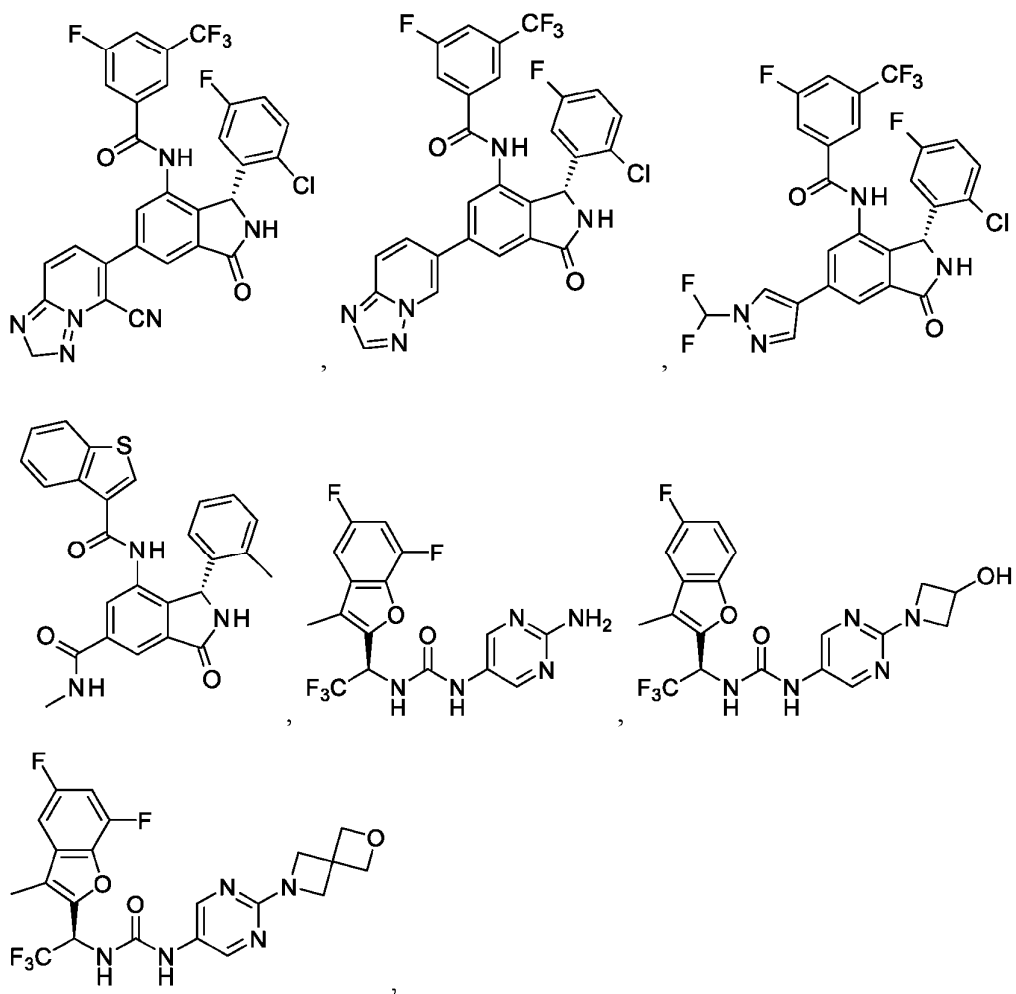


or pharmaceutically acceptable salt thereof, wherein **R**, **R₁**, **R₂**, **R₃**, **R₄**, **R₅**, **R₆**, **R₇**, and **R₈**, are as defined in claim 45, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a blood sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of compound of Formula I or pharmaceutically acceptable salt thereof to the patient if the patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation.

64. A PI3K α specific inhibitor selected from alpelisib and inavolisib, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of alpelisib, inavolisib, or a pharmaceutically acceptable salt thereof to the patient if the patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present.

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65. A PI3K α specific inhibitor that binds to PI3K α allosteric pocket 2 selected from

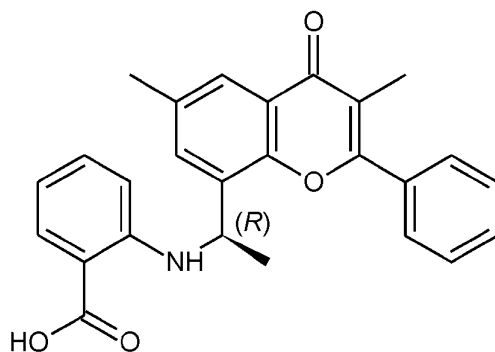


and pharmaceutically acceptable salts thereof, for use in the treatment of a disease or disorder associated with modulation of phosphatidylinositol 3-kinase alpha (PI3K α) in a patient in need thereof, comprising assaying a blood sample from a patient, determining if a patient has a cancer comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation, and administering a therapeutically effective amount of the PI3K α specific inhibitor or pharmaceutically acceptable salt thereof to the patient if the patient has a cancer

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comprising an M1043I/L in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047 mutation is present.

66. A compound for use according to any one of 45-58, 60, 62, and 63, wherein the compound of Formula I is of the formula:



or a pharmaceutically acceptable salt thereof.

67. A compound for use according to any one of 45-58, 60, 62, and 63, wherein the therapeutically effective amount of the compound of Formula I administered to the patient is a 100-1200 mg oral dose administered two times daily.

68. A compound for use according to any one of 45-58, 60, 62, and 63, wherein the therapeutically effective amount of the compound of Formula I administered to the patient is a 9-75 mg/kg oral dose administered two times daily.

69. A compound for use according to any of claims 45-68, wherein the disease or disorder is cancer.

70. A compound for use according to any of claims 45-69, wherein the disease or disorder is breast cancer.

71. A compound for use according to any of claims 45-70, wherein the disease or disorder is PIK3CA-mutated, advanced, or metastatic breast cancer.

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72. A compound for use according to any of claims 45-71, wherein the disease or disorder is PIK3CACA H1047R-mutant advanced, or metastatic breast cancer.

73. A compound for use according to claim 72, wherein the PIK3CACA H1047R-mutant advanced, or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

74. A compound for use according to any of claims 45-73, wherein the patient is a postmenopausal female.

75. A compound for use according to any of claims 45-74, wherein the patient has type II diabetes mellitus.

76. A compound for use according to any of claims 45-75, further comprising administering to the patient a therapeutically effective amount of a selective estrogen receptor degrader (SERD).

77. A compound for use according to claim 76, wherein the SERD is selected from imlunestrant, fulvestrant, giredestrant, amcenenestrant, rintodestrant, elacestrant, camizestrant, LSZ102, Zn-c5, and D-0502.

78. A compound for use according to claim 76 or 77, wherein the therapeutically effective amount of the SERD is a 500 mg dose administered on days 1, 15, and 29.

79. A compound for use according to any one of claims 45-78, wherein the second PI3K α specific inhibitor is administered after the disease or disorder has developed resistance to the first PI3K α specific inhibitor.