potentially be mitogenic and/or antiapoptotic for cancer cells, and thus negate the antiproliferative effects of PI3K inhibitors (Blouin M-J, et al, Abstract 4615: the hyperinsulinemia caused by PI3K inhibitors attenuates their antineoplastic efficacy, but can be minimized by co-administration of metformin. Cancer Res 2013;73:4615).

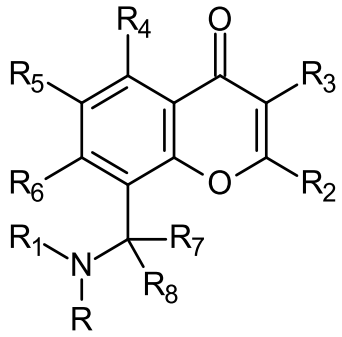
[12] In the setting of cancer with mutated PI3Kα, one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic PI3Kα inhibition would be to develop inhibitors with enhanced selectivity for mutant PI3Kα over wild-type PI3Kα. This would create an increased window for drug dosing to selectively inhibit the pathologic signaling of mutant PI3Kα in the cancer cells without affecting the wild-type PI3Kα in the host tissues that control systemic metabolism (Okkenhaug K, Graupera M, Vanhaesebroeck B. Targeting PI3K in Cancer: Impact on Tumor Cells, Their Protective Stroma, Angiogenesis, and Immunotherapy. Cancer Discov. 2016 Oct;6(10):1090-1105), thus limiting toxicities, and permitting higher doses, and more complete inhibition of the drug target (Ariella B. Hanker, et al, Challenges for the clinical development of PI3K inhibitors: Strategies to improve their impact in solid tumors. Cancer Discov. 2019 Apr; 9(4): 482–491).

[13] Currently PI3Kα inhibitors are nearly equipotent to wild-type, and mutant PI3Kα. Mutant selective inhibitors have been elusive due to the PI3Kα mutations location far from the active site. As such, inhibitors which target a second, peripheral binding pocket near a known mutation (e.g., H1047R) may provide a route to selective PI3Kα inhibition. Thus, targeting a mutated, peripheral binding pocket of PI3Kα, provides a valuable therapeutic target for drug development.

[14] As such, kinases, for example lipid kinases such as PI3Ks, are prime targets for drug development. The present invention provides a new class of kinase inhibitors.

Summary

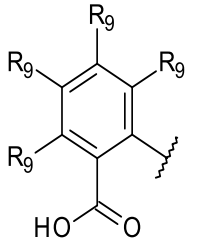
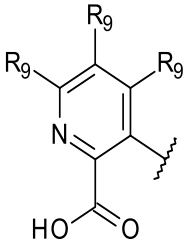
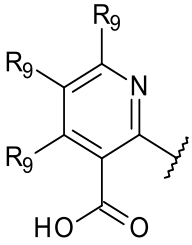
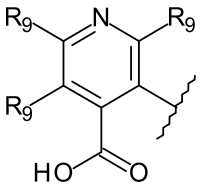
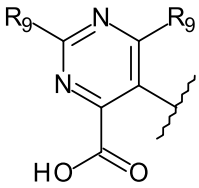
[14a] In a first aspect of the present disclosure, there is provided a compound of the Formula:

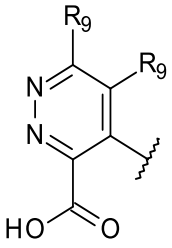
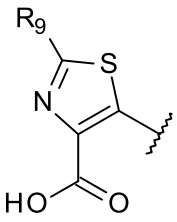


or pharmaceutically acceptable salt thereof, wherein:

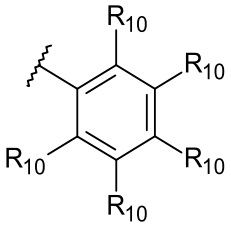
R is -H or C_1-C_3 alkyl;

R_1 is a group of the formula:


; 
; 
; 
; 
;


; or 
;

R_2 is a group of the formula:


;

R_3 is -H, halogen, -CN, -N(H)(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -N(H)($CH_2CH_2CO_2H$), -C(O)C_1-C_3 alkyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_5 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, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

each of **R_4**, **R_5** and **R_6** is independently -H, halogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R_7 is -CN, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

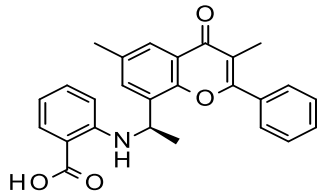
R_8 is -H or C_1-C_6 alkyl;

each **R_9** is independently -H, halogen, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_3-C_5 cycloalkyl;

each **R_{10}** is independently -H, -CN, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -SO_2R_{11}, -$C(O)OC_1$-C_3 alkyl, -$CONR_{11}R_{11}$, -$NR_{11}R_{11}$, -NR_{11}-CO_2R_{11}, -OH, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C_1-C_3 alkoxy, or -$CONR_{11}R_{11}$; the optionally substituted C_3-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, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -SO_2R_{11}, -$NR_{11}R_{11}$, -OH or -CN; and

each **R_{11}** is independently -H or C_1-C_3 alkyl.

[14b] In another aspect of the present disclosure, there is provided a compound that is



; or a pharmaceutically acceptable salt thereof.

[14c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[14d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

[14e] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in treating a disease or disorder associated with modulating PI3K.

[14f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease associated with modulating PI3K.

[15] In one example, the present disclosure relates to compounds of Formula (I):

optionally substituted heterocycle or heteroaryl is each optionally substituted with one to three substituents each independently selected from halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

each of **R_4**, **R_5** and **R_6** is independently -H, halogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R_7 is -CN, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R_8 is -H or C_1-C_6 alkyl;

each **R_9** is independently -H, halogen, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_3-C_5 cycloalkyl;

each **R_{10}** is independently -H, -CN, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -SO_2R_{11}, -C(O)OC_1-C_3 alkyl, -$CONR_{11}R_{11}$, -$NR_{11}R_{11}$, -NR_{11}-CO_2R_{11}, -OH, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C_1-C_3 alkoxy, or -$CONR_{11}R_{11}$; the optionally substituted C_3-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, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -SO_2R_{11}, -$NR_{11}R_{11}$, -OH or -CN; and

each **R_{11}** is independently -H or C_1-C_3 alkyl.

[16] In another example, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, or carrier.

[17] In another example, the present disclosure provides a method of modulating PI3K (e.g., PI3Kα) 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.

[18] In some examples, the present disclosure provides a method of treating, or preventing a disease, or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a

pharmaceutically acceptable salt thereof.

[19] In some examples, the present disclosure provides a method of treating, or preventing a disease, or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof.

[20] In some examples, the present disclosure provides a method of treating a disease, or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof.

[21] In some examples, the present disclosure provides a method of treating a disease, or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof.

[22] In another example, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof for use in therapy.

[23] In another example, 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., PI3Kα) activity (e.g., *in vitro*, or *in vivo*).

[24] In another example, the present disclosure provides a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, for use in selective inhibition for mutant PI3Kα over wild-type PI3Kα.

[25] In another example, 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.

[26] In another example, 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.

[27] In another example, 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., PI3Kα) activity (e.g., *in vitro*, or *in vivo*).

[28] In another example, 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.

[29] In another example, 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.

[30] In another example, the present disclosure provides a method of preparing a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof.

[31] In another example, the present disclosure provides a method of preparing a compound, comprising one, or more steps described herein.

[32] In another example, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound as described herein (e.g., a method comprising one, or more steps described in the Schemes).

[33] In another example, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein (e.g., the intermediate is selected from the intermediates described in the Examples).

[34] Other features, and advantages of the disclosure will be apparent from the following detailed description, and claims.

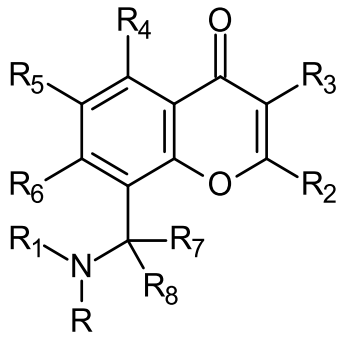
Detailed Description

[35] The present invention provides 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 by administering to a patient in need thereof a therapeutically effective amount of a PI3K inhibitor of the present invention. The methods (or uses) of the present invention can be used in the treatment of a variety of PI3K-dependent diseases, and disorders.

[36] In some embodiments, the disease, or disorder is a cancer (e.g., 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

CLAIMS:

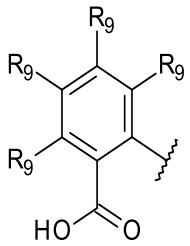
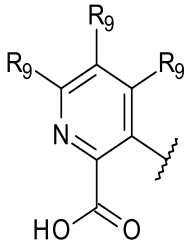
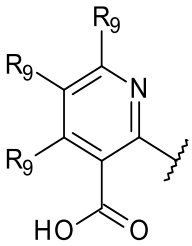
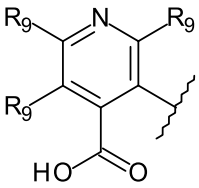
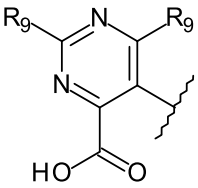
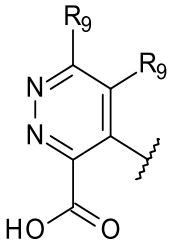
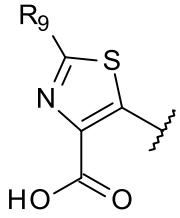
1. A compound of the Formula:



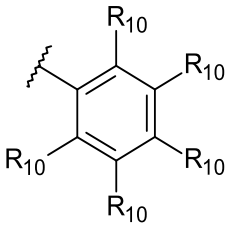
or pharmaceutically acceptable salt thereof, wherein:

R is -H or C_1-C_3 alkyl;

R_1 is a group of the formula:


;

;

;

;

;

; or

;

R_2 is a group of the formula:


;

R_3 is -H, halogen, -CN, -N(H)(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -N(H)($CH_2CH_2CO_2H$), -C(O)C_1-C_3 alkyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_5 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, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

each of **R_4**, **R_5** and **R_6** is independently -H, halogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R_7 is -CN, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

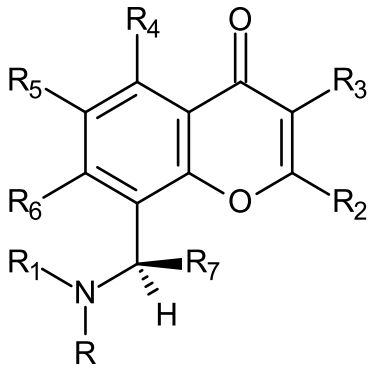
R_8 is -H or C_1-C_6 alkyl;

each **R_9** is independently -H, halogen, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_3-C_5 cycloalkyl;

each **R_{10}** is independently -H, -CN, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -SO_2R_{11}, -C(O)OC_1-C_3 alkyl, -$CONR_{11}R_{11}$, -$NR_{11}R_{11}$, -NR_{11}-CO_2R_{11}, -OH, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, C_1-C_3 alkoxy, or -$CONR_{11}R_{11}$; the optionally substituted C_3-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, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -SO_2R_{11}, -$NR_{11}R_{11}$, -OH or -CN; and

each **R_{11}** is independently -H or C_1-C_3 alkyl.

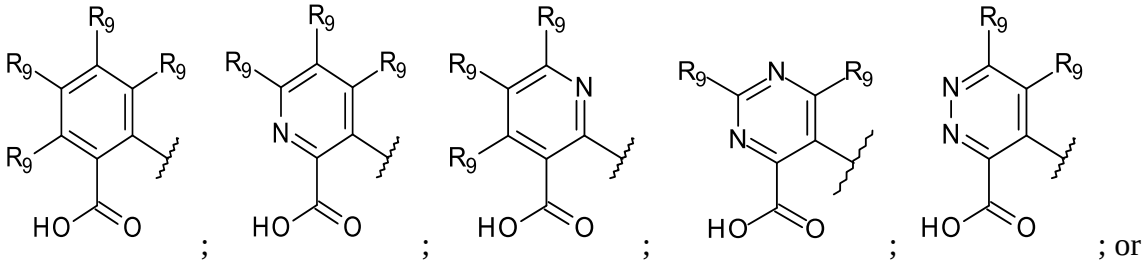
2. The compound of claim 1, or pharmaceutically acceptable salt thereof, having the Formula:



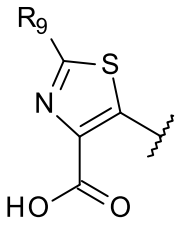
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3. The compound of claim 1 or claim 2, or pharmaceutically acceptable salt thereof, wherein **R** is -H.

4. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_1}$ is a group of the formula:

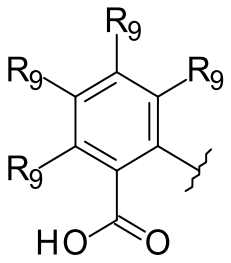


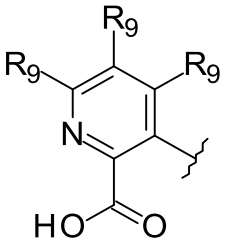
; ; ; ; ; or

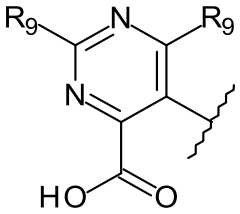


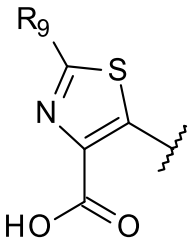
.

5. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_1}$ is a group of the formula:



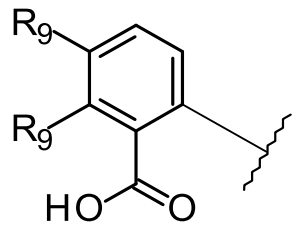
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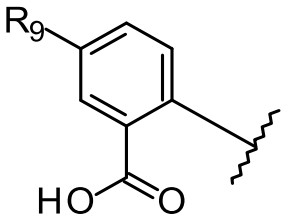
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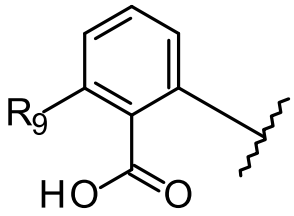
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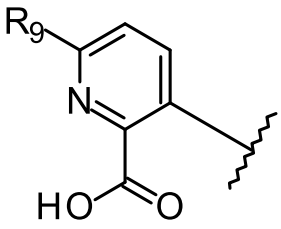
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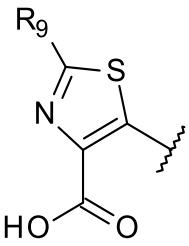
6. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein **R_1** is a group of the formula:

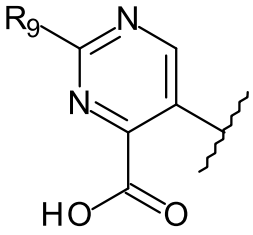


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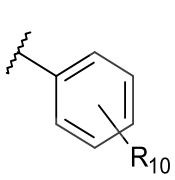
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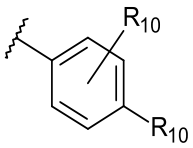
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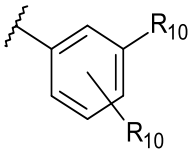
7. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein each **R_9** is independently -H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_3-C_5 cycloalkyl.

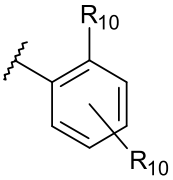
8. The compound of any one of claims 1-7, or pharmaceutically acceptable salt thereof, wherein each **R_9** is independently -H, halogen, C_1-C_3 alkyl or C_1-C_3 haloalkyl.

9. The compound of any one of claims 1-8, or pharmaceutically acceptable salt thereof, wherein **R_2** is a group of the formula:



; 

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; or 

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10. The compound of any one of claims 1-9, or pharmaceutically acceptable salt thereof, wherein each **R_{10}** is independently -H, -CN, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -SO_2R_{11}, -$CONR_{11}R_{11}$, -$NR_{11}R_{11}$, -NR_{11}-CO_2R_{11}, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C_1-C_3 alkoxy; the optionally substituted C_3-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, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, -SO_2R_{11}, -$NR_{11}R_{11}$, -OH or -CN.

11. The compound of any one of claims 1-9, or pharmaceutically acceptable salt thereof, wherein each **R_{10}** is independently -H, -CN, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -SO_2R_{11}, -$CONR_{11}R_{11}$, -$NR_{11}R_{11}$, -NR_{11}-CO_2R_{11}, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_3-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is each optionally substituted with a -CN, -OH, oxetanyl, or C_1-C_3 alkoxy; the optionally substituted C_3-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, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, $-SO_2R_{11}$, $-NR_{11}R_{11}$, -OH or -CN.

12. The compound of any one of claims 1-11, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_3}$ is -H, –CN, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

13. The compound of any one of claims 1-12, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_3}$ is -H or methyl.

14. The compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_4}$ is -H.

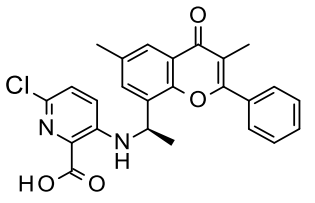
15. The compound of any one of claims 1-14, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_5}$ is -H, halogen, C_1-C_3 alkyl or C_1-C_3 haloalkyl.

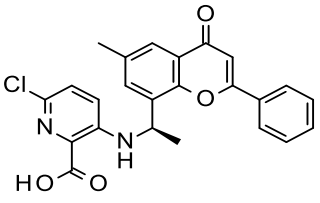
16. The compound of any one of claims 1-15, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_6}$ is -H or halogen.

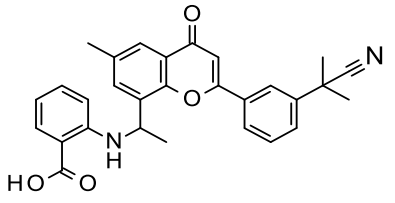
17. The compound of any one of claims 1-16, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_7}$ is methyl.

18. The compound of any one of claims 1 or 3-17, or pharmaceutically acceptable salt thereof, wherein $\mathbf{R_8}$ is H.

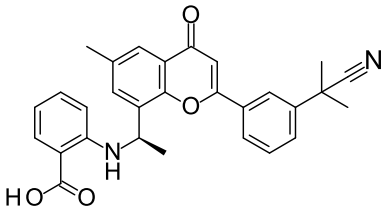
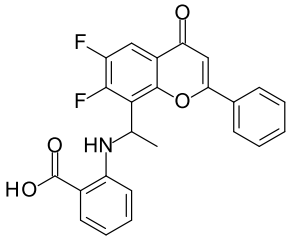
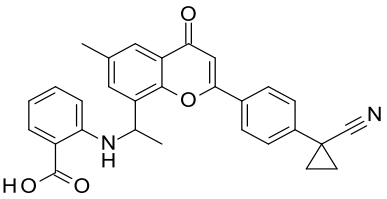
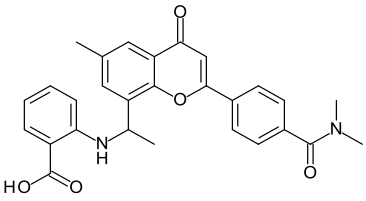
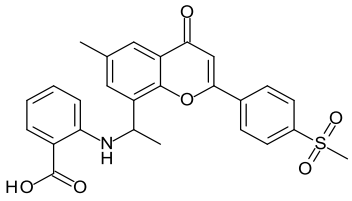
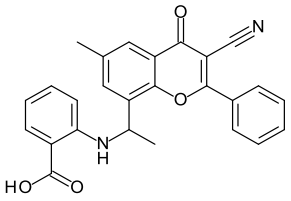
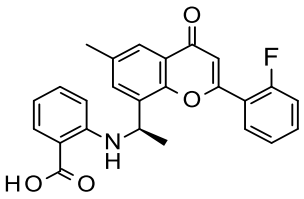
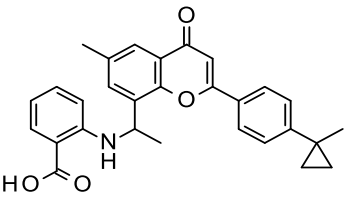
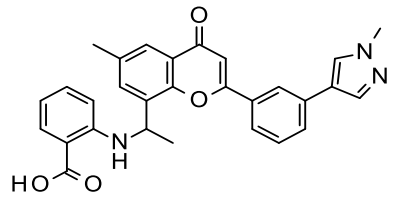
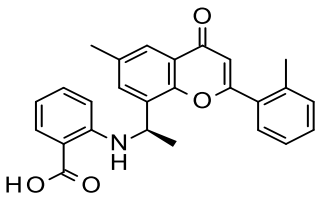
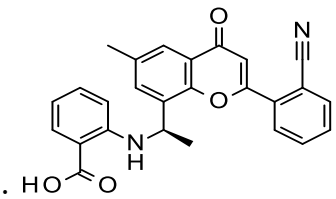
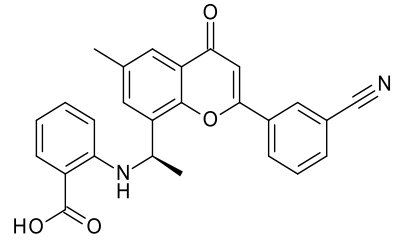
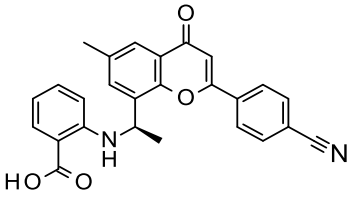
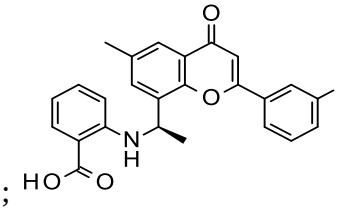
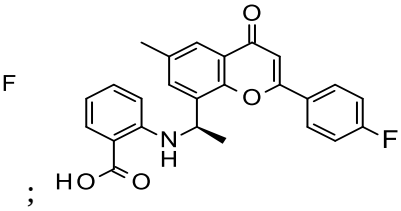
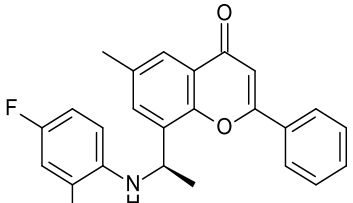
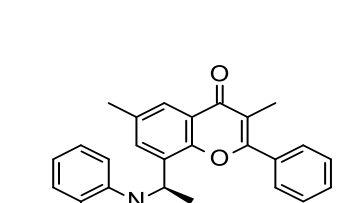
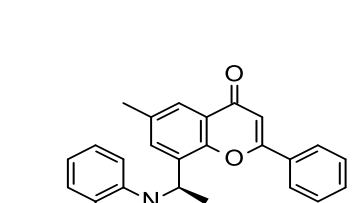
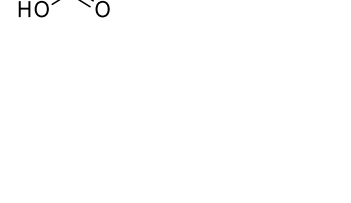
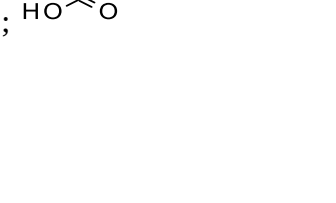
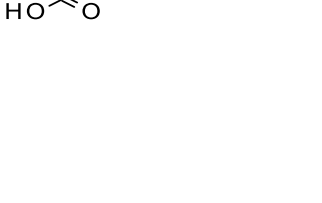
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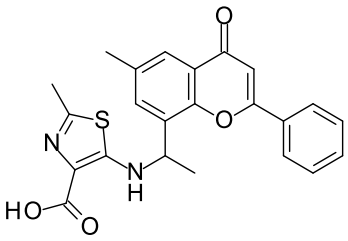
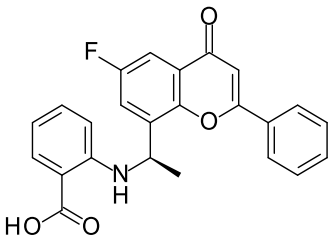
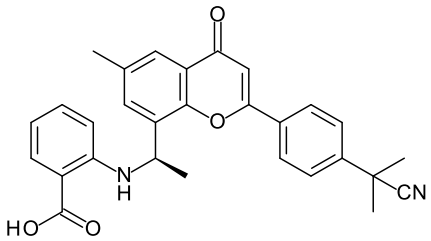


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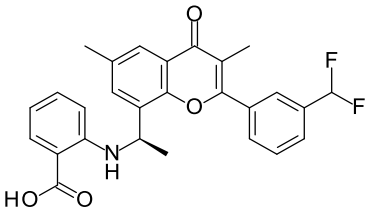
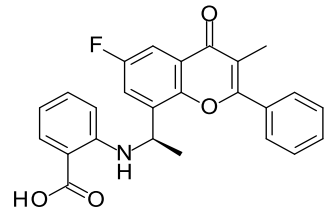
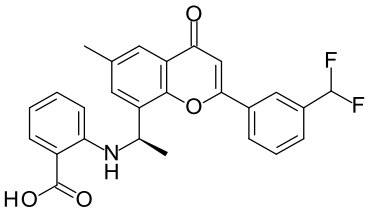

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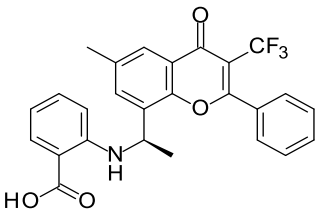
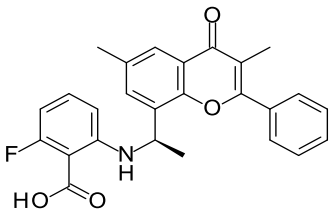
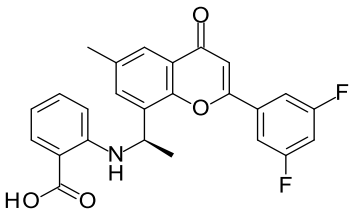


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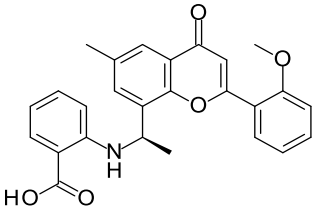
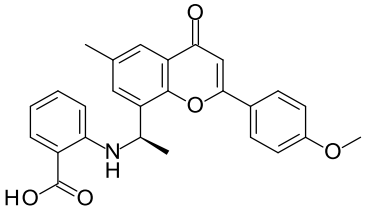
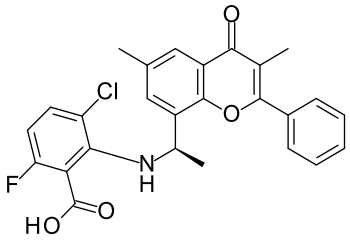
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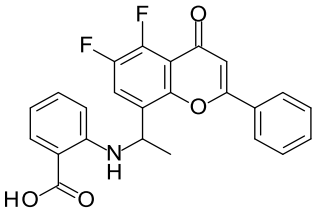
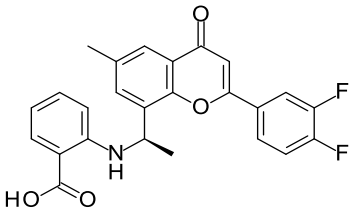
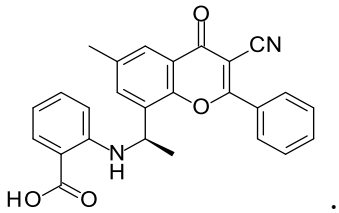
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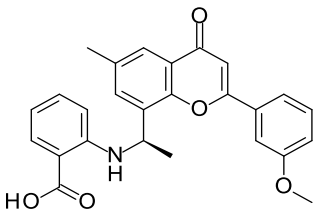
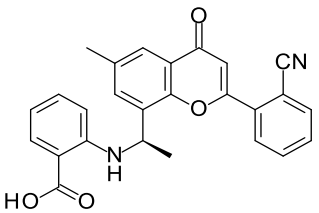
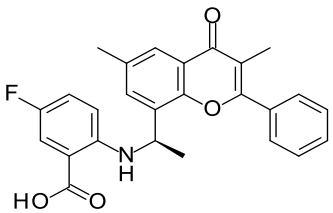
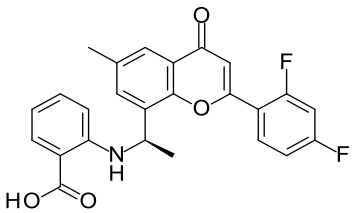
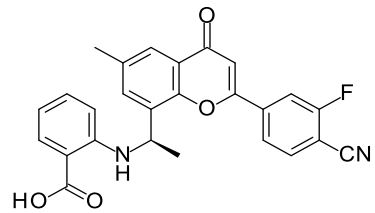
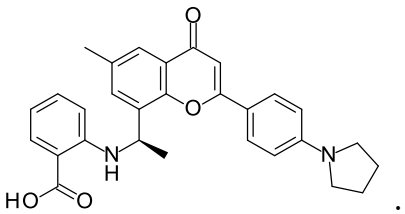
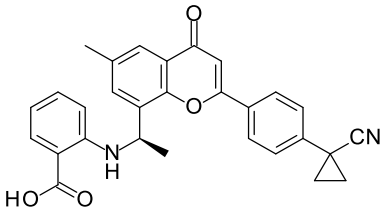
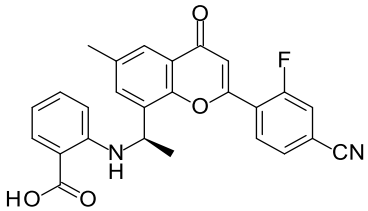
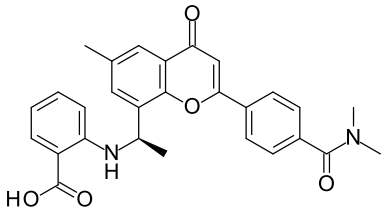
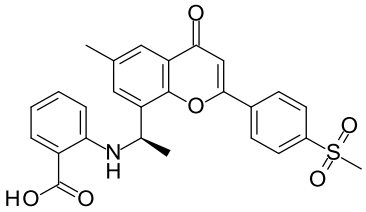
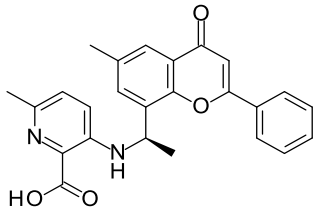
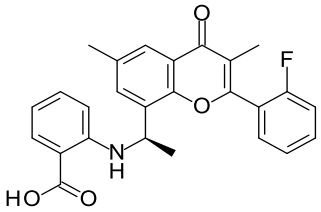
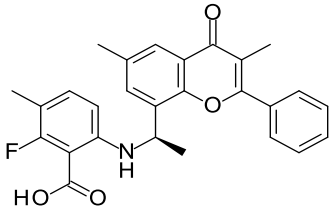
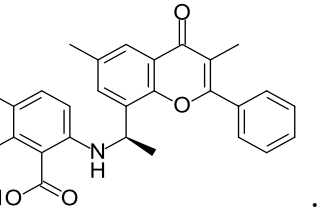
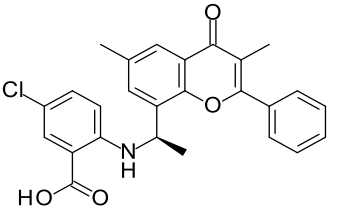
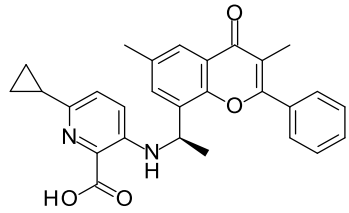
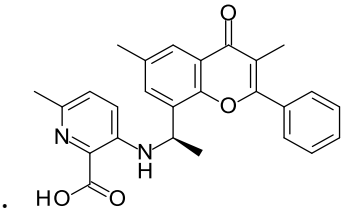
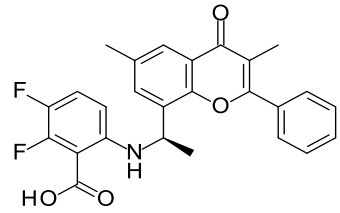
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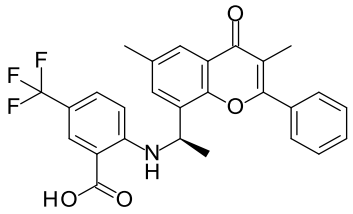
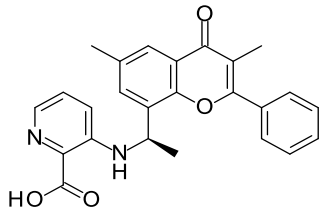
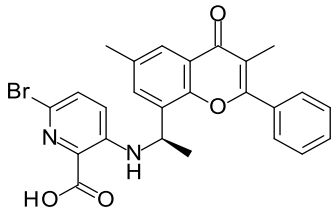

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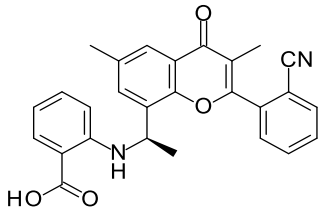
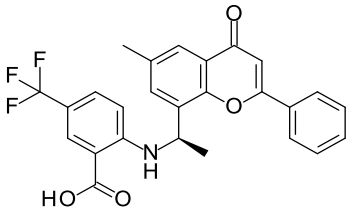
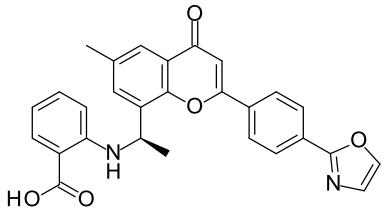

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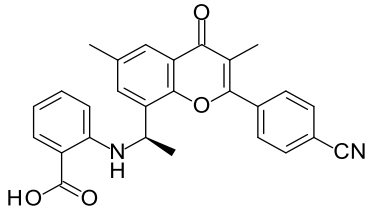
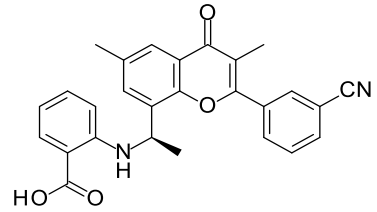
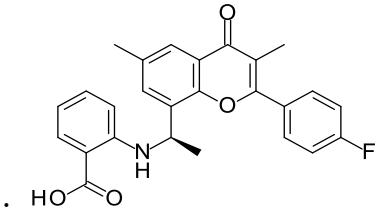
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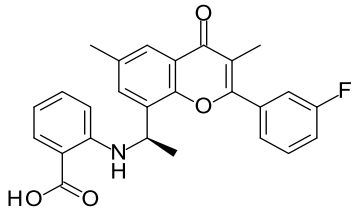
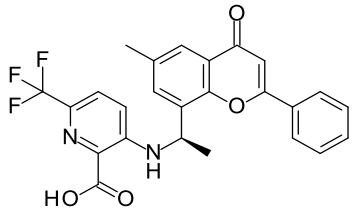
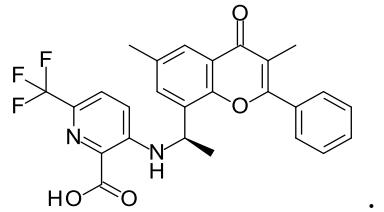
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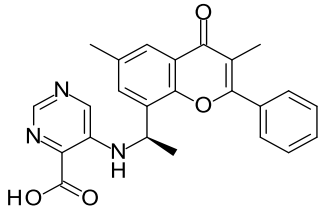
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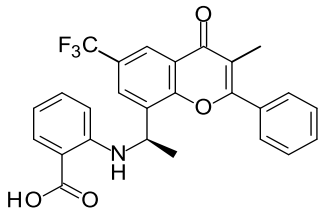
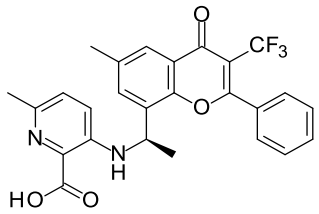
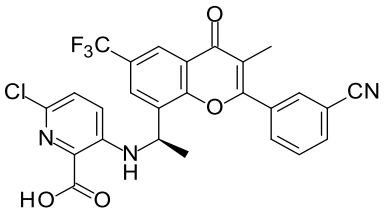

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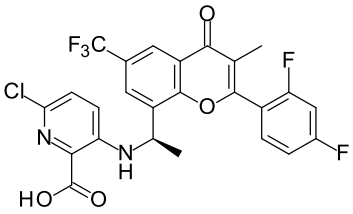
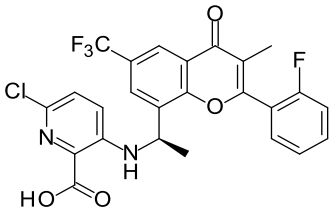
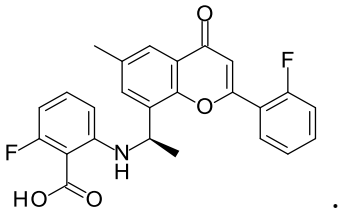
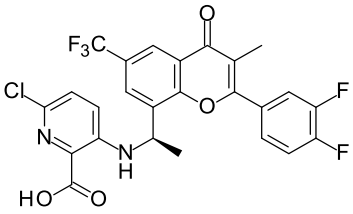
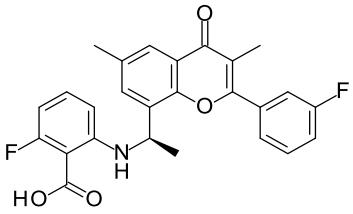
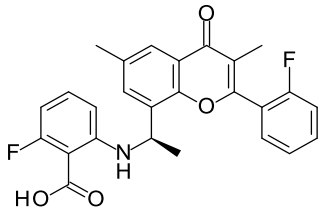
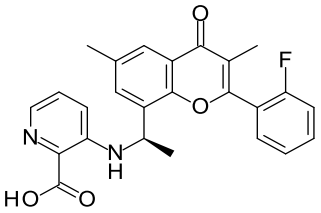
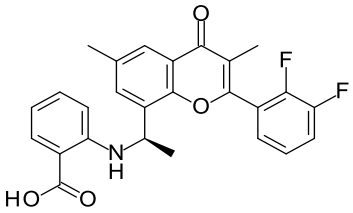
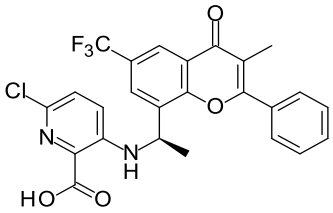
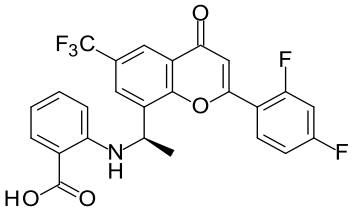
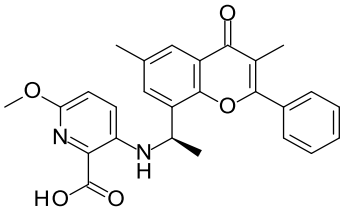
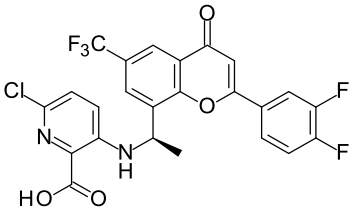
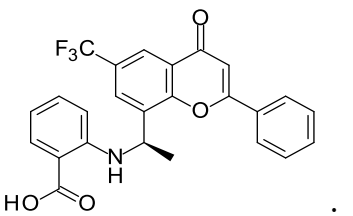
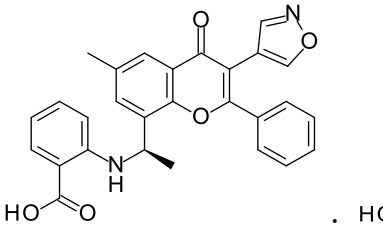
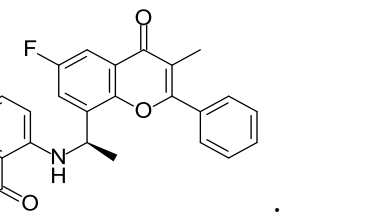
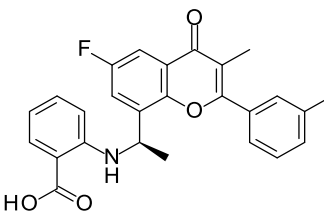
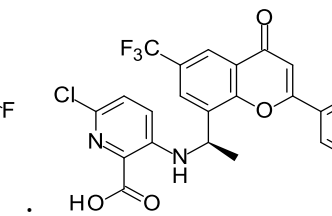
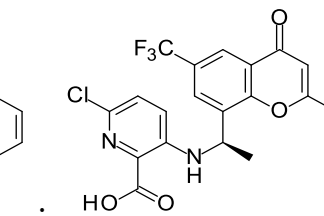

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or a pharmaceutically acceptable salt thereof.

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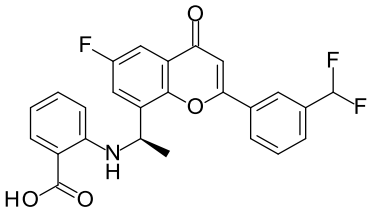

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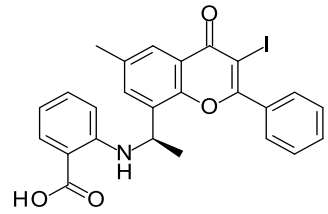

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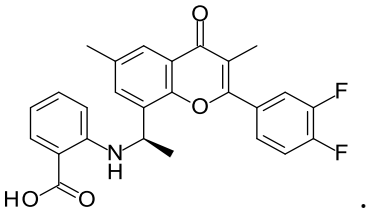
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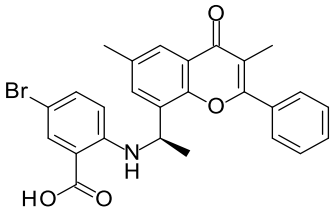
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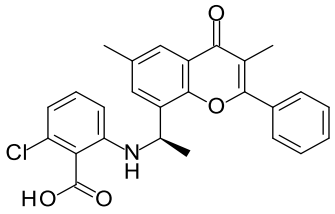


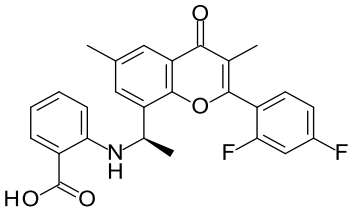
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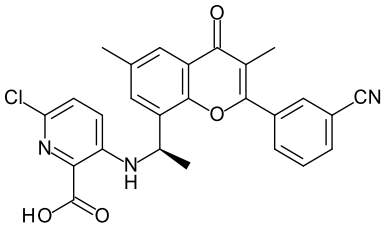
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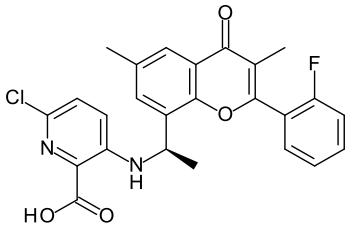
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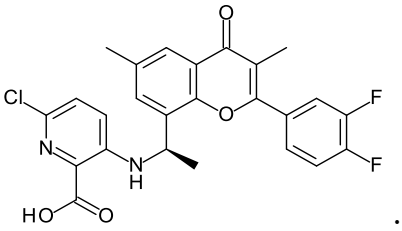
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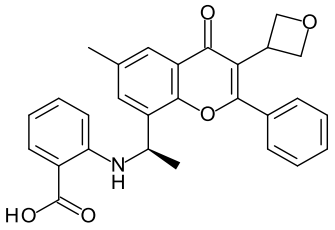
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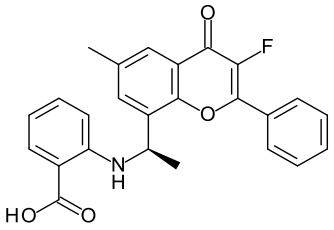


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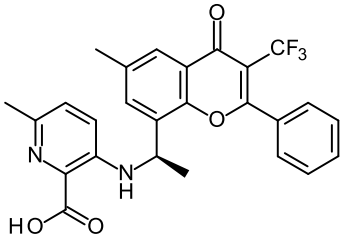


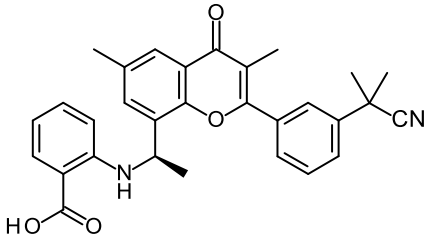
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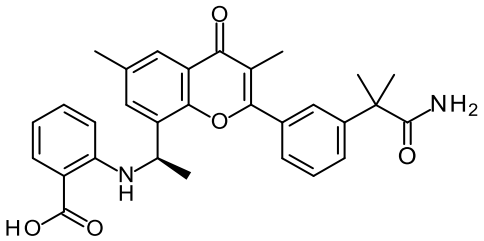
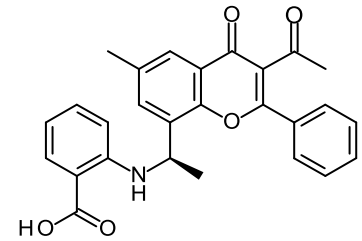
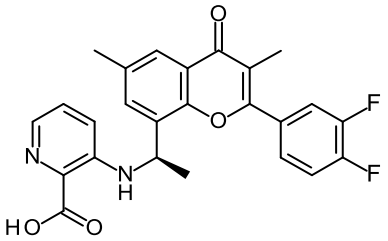
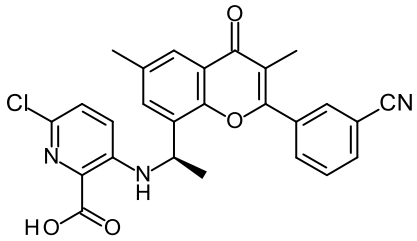
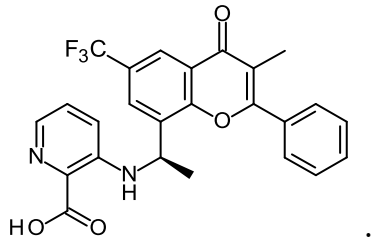
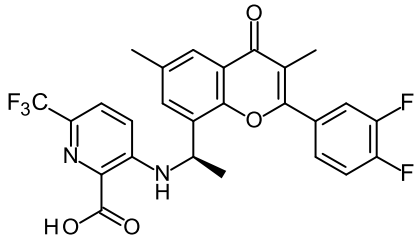
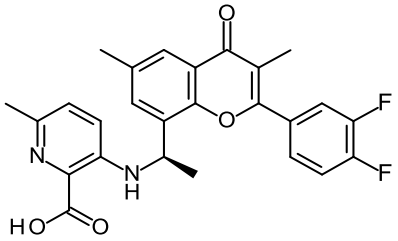
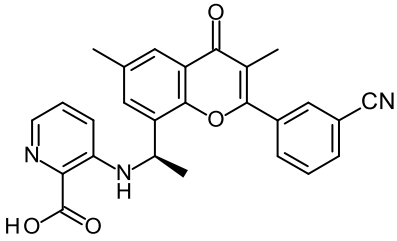
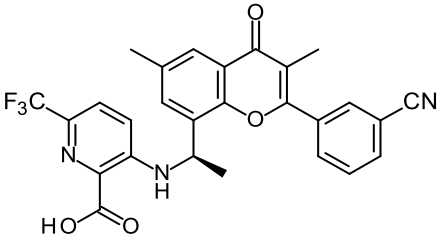
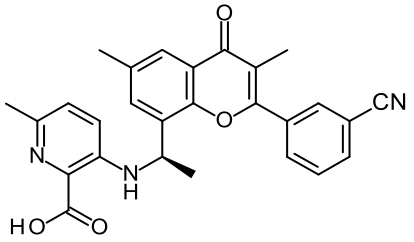
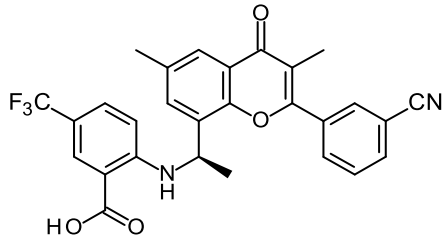
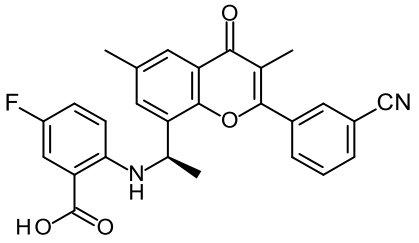
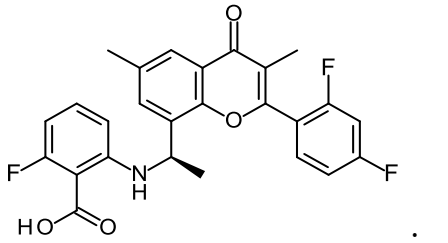
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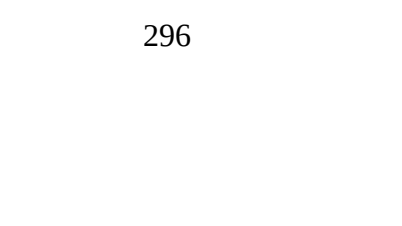
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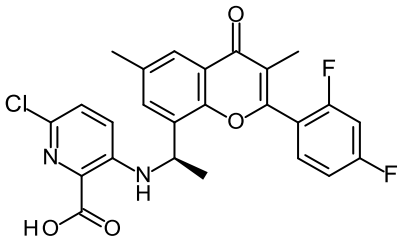
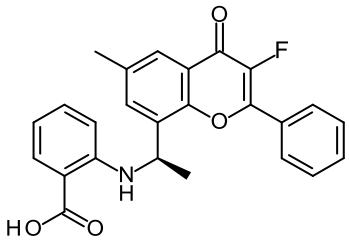
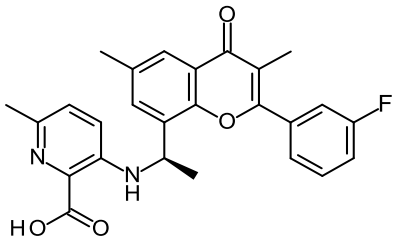
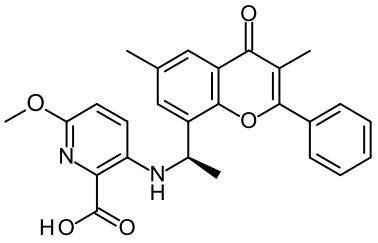
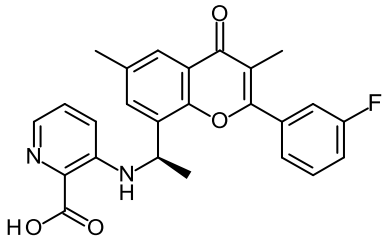
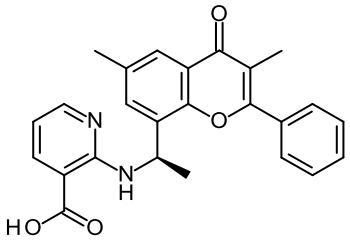
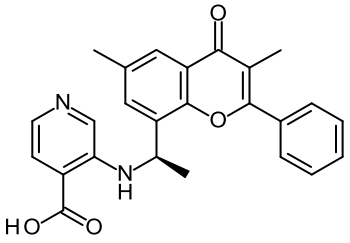
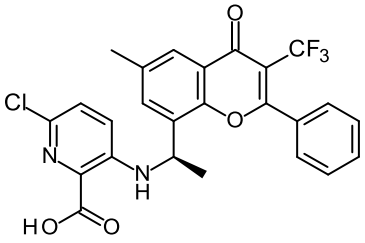
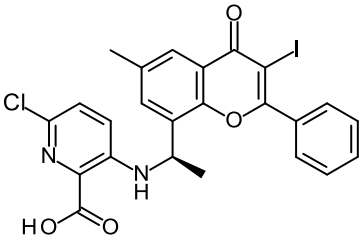
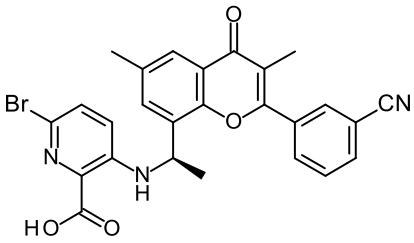
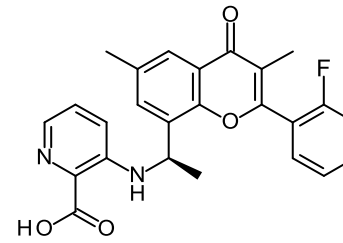


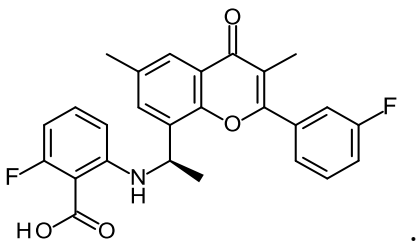
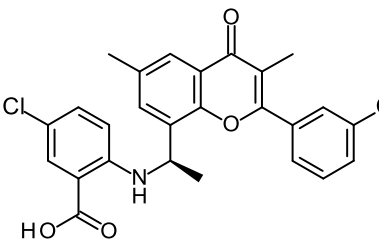
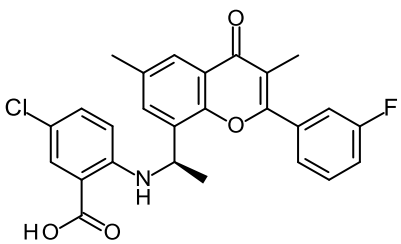
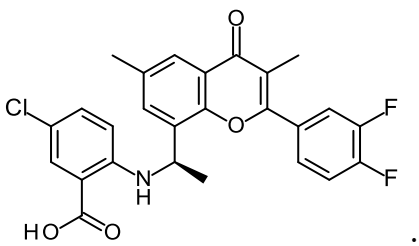
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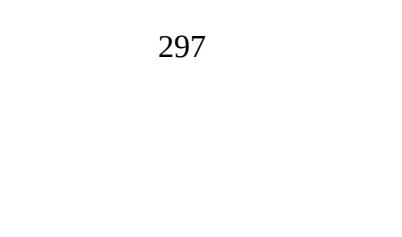
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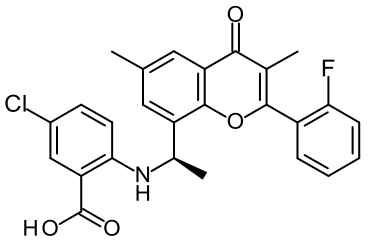
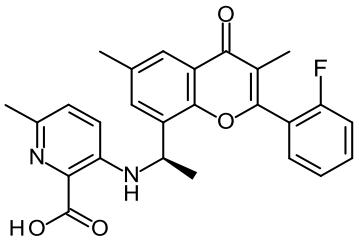
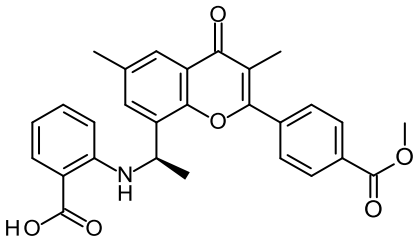
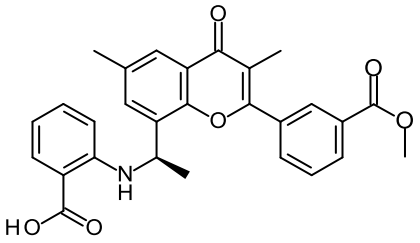
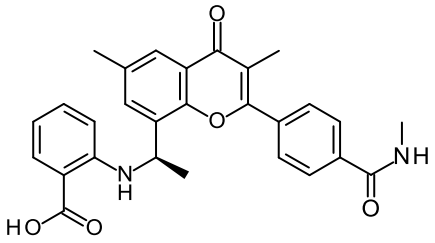
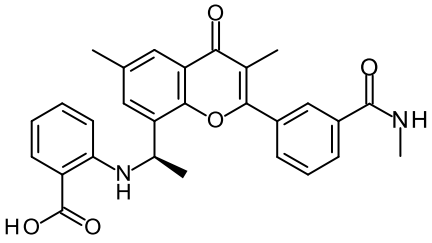
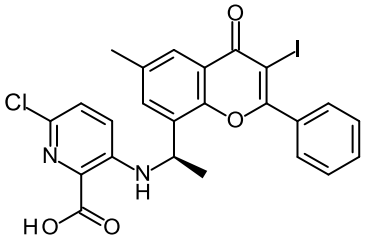
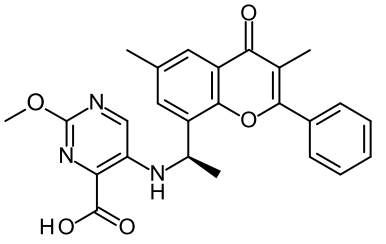
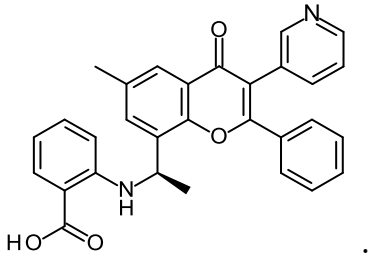
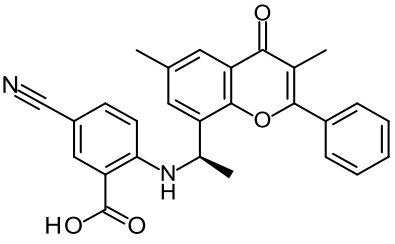
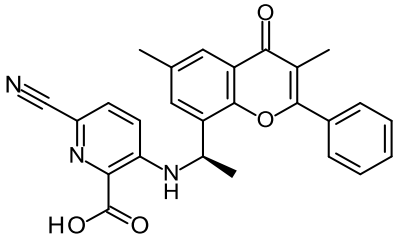
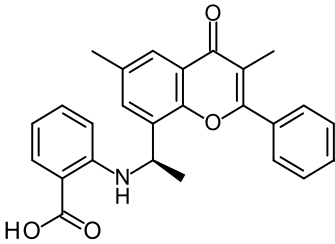

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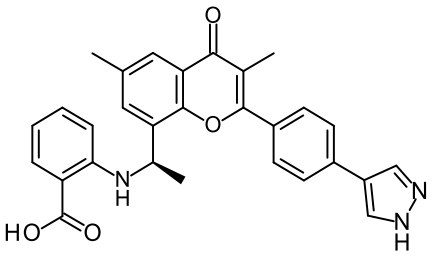
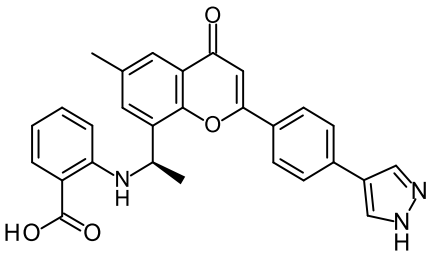
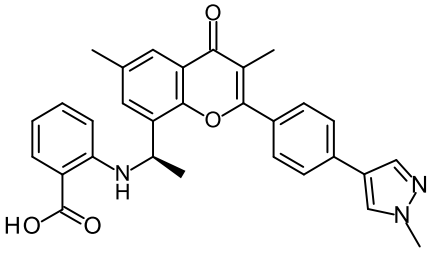
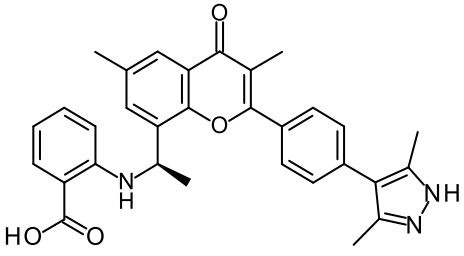
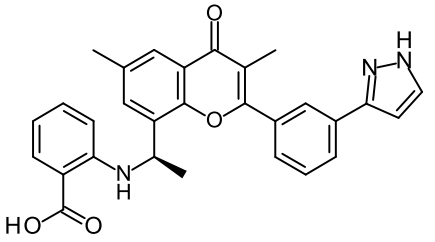
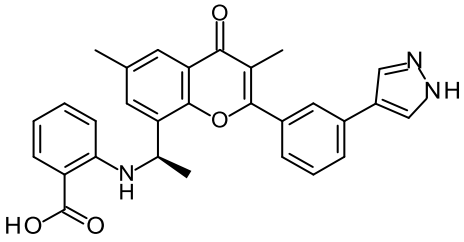
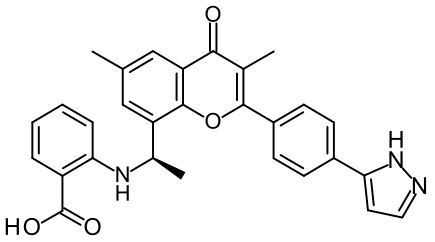
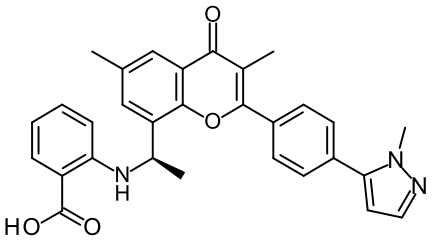
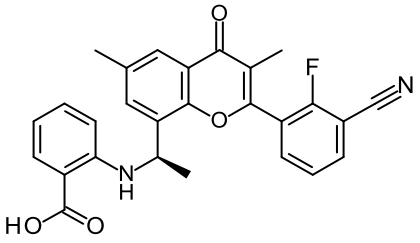
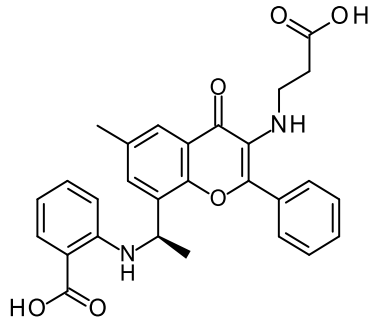
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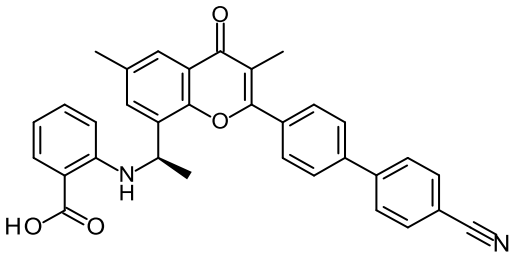
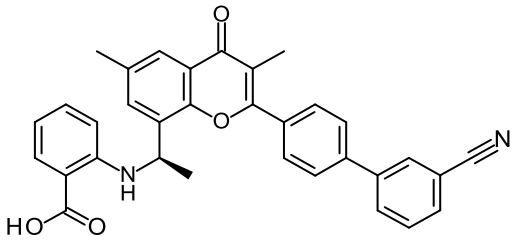
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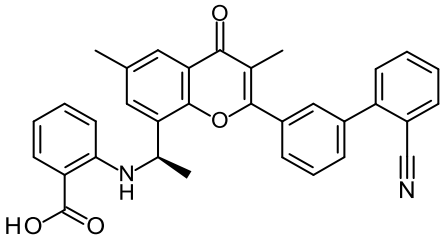
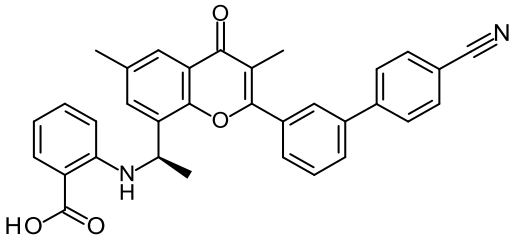

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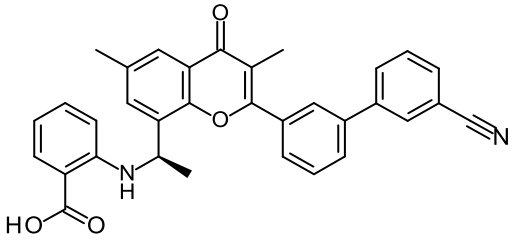
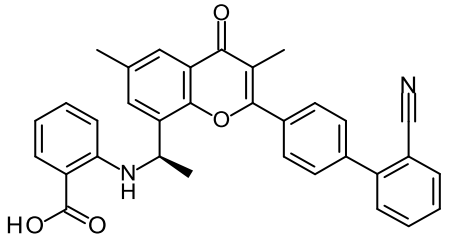
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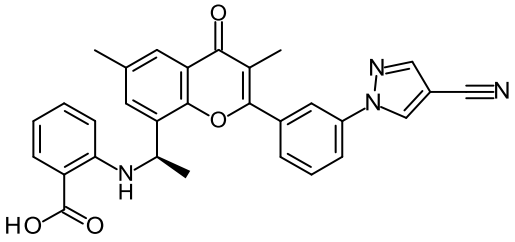
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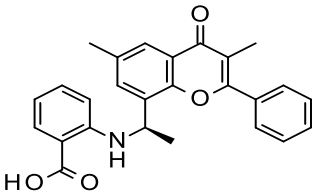

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or a pharmaceutically acceptable salt thereof.

24. A compound that is


; or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

26. A compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 25, for use in therapy.

27. A compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 25, for use in treating a disease or disorder associated with modulating PI3K.

28. The compound or composition for use of claim 27, wherein the disease associated with modulating PI3K is a cancer.

29. The compound or composition for use of claim 28, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

30. The compound or composition for use of claim 28, wherein the cancer is breast cancer.

31. The compound or composition for use of claim 28, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

32. The compound or composition for use of claim 27, wherein the disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndromes (PROS).

33. Use of a compound of any one of claims 1-24, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 25, in the manufacture of a medicament for the treatment of a disease associated with modulating PI3K.

34. The use of claim 33, wherein the disease associated with modulating PI3K is a cancer.

35. The use of claim 34, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

36. The use of claim 34, wherein the cancer is breast cancer.

37. The use of claim 34, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

38. The use of claim 33, wherein the disease is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndromes (PROS).