COMPOSITIONS AND METHODS FOR USE IN THE TREATMENT OF CANCER AND OTHER INDICATIONS

GOVERNMENT SUPPORT

[0001] This invention was made with government support under Contract No. DE-AC52-07NA27344 awarded by the United States Department of Energy. The government has certain rights in the invention.

RELATED APPLICATIONS

[0002] This application claims priority to and benefit of U.S. Application No. 63/307,882, filed February 8, 2022, and U.S. Application No. 63/416,772, filed October 17, 2022, the entire contents of each of which are hereby incorporated by reference.

BACKGROUND

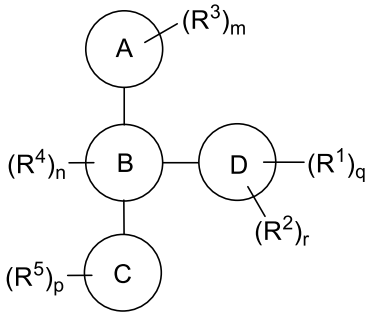
[0003] An estimated over 600,000 Americans will have died from cancer in 2021, corresponding to more than 1600 deaths per day (Cancer Facts and Figures 2021). The greatest number of deaths are from cancers of the lung, prostate, and colorectum in men, and cancers of the lung, breast, and colorectum in women. Almost one-quarter of all cancer deaths are due to lung cancer, 82% of which is directly caused by cigarette smoking. The 5-year survival rate for lung cancer patients is only about 20%.

[0004] The aberrant activation of the phosphoinositide 3-kinase (PI3K) is one of the most frequent oncogenic events across human cancers, and its inhibition is an attractive therapeutic approach in treating cancers. PI3Ks signal downstream of receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), and RAS proteins to regulate a large number of cellular activities, including metabolism, proliferation, and migration.

[0005] The frequency of PI3K oncogenic events has fueled the development and testing of PI3K inhibitors. Most PI3K inhibitors that have entered clinical development thus far are reversible, ATP-competitive kinase inhibitors. Despite considerable efforts, the clinical outcome of PI3K inhibitor-based treatments for solid tumors has been disappointing, mainly due to intolerable toxicity and drug resistance.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a compound of formula I:



I

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

Ring A is selected from phenyl and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is a 9- to 10-membered bicyclic ring that comprises at least one 5- or 6-membered heteroaryl ring;

Ring C is selected from phenyl; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 8-membered bicyclic carbocyclic ring; a 4- to 8-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7- to 10-membered spirofused heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each of the phenyl, heteroaryl, and heterocyclic rings is optionally fused to Ring E;

Ring D is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and phenyl, wherein each of the heteroaryl and phenyl rings is optionally fused to Ring F;

Ring E is selected from a 5- to 6-membered carbocyclic ring; a 5- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 7- to 10-membered spirofused heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring E is substituted by s instances of $R^{5'}$;

Ring F is selected from phenyl; a 5- to 6-membered carbocyclic ring; a 5- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring F is substituted by u instances of –L-W and y instances of $R^{2'}$;

R^1 is selected from –L-W, Ring D′, or a bivalent C_{1-6} aliphatic chain substituted with Ring D′;

each –L-W is –CN, or:

each L is independently a bivalent straight or branched C_{1-8} aliphatic chain wherein one or more methylene units of the aliphatic chain are optionally and independently replaced by a group selected from -N(R)-, -O-, -S-, -C(O)-, -SO_2-, -CH(X)-, -$C(X)_2$-, -C(O)N(R)-, -N(R)C(O)-, -C(O)O-, -OC(O)-, -SO_2N(R)-, and -N(R)SO_2-;

each W is independently hydrogen, halogen, -CN, or an optionally substituted 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each X is independently halogen, -OR, or -CN;

each Ring D′ is independently a 4- to 6-membered carbocyclic ring or a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring D′ is substituted with t instances of –L-W;

each R^2 and $R^{2'}$ is independently selected from oxo, halogen, -CN, -OR, and C_{1-6} alkyl;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -O$(CH_2)_v$Cy, -OCH_2CH_2OR, and optionally substituted C_{1-6} aliphatic;

each Cy is independently a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3- to 6-membered carbocyclic ring; or a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-2 instances of R^6;

each R^4 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each of R^5 and $R^{5'}$ is independently selected from oxo, =NH, -CN, halogen, -OR, -N$(R)_2$, -SR, -C(O)R, -N(R)C(O)R, -$(CH_2)_x$C(O)N$(R)_2$, -C(O)N$(R)_2$, -C(O)N(R)$(CH_2)_x$Cy, -$(CH_2)_x$C(O)Cy, -OC(O)R, -C(O)OR, -SO_2R, -N(R)SO_2R, -N=S(O)$(R)_2$, -SO_2N$(R)_2$, -P(O)R_2, -$(CH_2)_x$Cy, -O$(CH_2)_x$Cy, and optionally substituted C_{1-6} aliphatic;

each R^6 is independently selected from oxo, -CN, halogen, -OR, -N$(R)_2$, -SR, -C(O)R, -N(R)C(O)R, -C(O)N$(R)_2$, -OC(O)R, -C(O)OR, -SO_2R, -N(R)SO_2R, -SO_2N$(R)_2$, and an optionally substituted group selected from C_{1-6} aliphatic; a 3- to 6-membered carbocyclic ring; phenyl; a 3- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 10-membered aryl ring; and a 9- to 10-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic; a 3- to 6-membered carbocyclic ring; phenyl; a 3- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 10-membered aryl ring; and a 9- to 10-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0 or 1;

r is 0, 1, or 2;

s is 0, 1, 2, or 3;

t is 0, 1, or 2;

u is 0 or 1;

each v is independently 0, 1, or 2;

each x is independently 0, 1, or 2; and

y is 0, 1, or 2.

[0005b] In another aspect of the present disclosure, there is provided a compound selected from Table 1, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0005c] In a further aspect of the present disclosure, there is provided a compound selected from Table 2, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable carrier or excipient.

[0005e] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease, disorder, or condition.

[0005f] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein, wherein the medicament is to be contacted with a cell containing the small GTPase and the PI3Kα protein.

[0005g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contacting a cell containing a small GTPase and a PI3Kα protein.

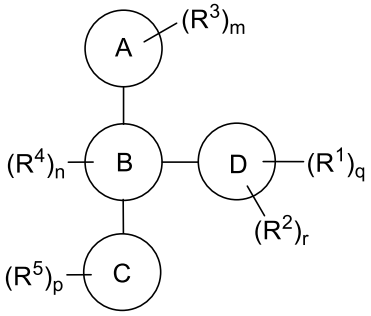
[0005h] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0006] The present disclosure provides new therapeutic modalities for treating cancers and other indications (e.g., cancers and other indications associated with and/or characterized by aberrant activation of PI3K). The present disclosure encompasses the recognition that a therapeutic agent (e.g., a therapeutic agent comprising a small molecule, e.g., a compound provided herein) that disrupts, inhibits, and/or prevents an interaction between a PI3K protein (e.g., PI3Kα) and a small GTPase (e.g., Rac1, CDC42, or a

RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) may be particularly useful for treating, ameliorating, delaying the progress of, ameliorating or eliminating a symptom of, and/or inhibiting a cancer and/or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K). Without wishing to be bound by theory, therapeutic agents provided herein (e.g., therapeutic agents comprising small molecules, e.g., compounds provided herein) may be capable of binding to a PI3K protein (e.g., PI3Kα) while displaying (i) no or minimal binding to a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and/or (ii) no substantial effect on the kinase activity of the PI3K protein (e.g., PI3Kα). In some examples, such therapeutic agents may provide advantages such as improved efficacy or reduced side effects as compared to, e.g., ATP-competitive PI3K kinase inhibitors, as described herein. For example, in some examples, such therapeutic agents may provide reduced instances of hyperglycemia and/or hyperinsulinemia relative to PI3K kinase inhibitors.

[0007] The present disclosure provides compounds (including in any available forms, such as salt forms) useful in disrupting, inhibiting, and/or preventing an interaction between a PI3K protein (e.g., PI3Kα) and a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1). In some examples, the present disclosure provides compounds capable of binding a PI3Kα protein, such that (i) the interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and the PI3Kα protein is disrupted, inhibited, and/or prevented; and/or (ii) the kinase activity of the PI3Kα protein is not inhibited. In some examples, such compounds are useful for treating a cancer or other indication, as described herein.

[0008] In an example, the present disclosure provides a compound of Formula I:



I

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein each of Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, q, and r is as defined herein. In some examples, a compound of Formula I is capable of binding a PI3Kα protein, such that (i) the interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and the PI3Kα

protein is disrupted, inhibited, and/or prevented; and/or (ii) the kinase activity of the PI3Kα protein is not inhibited.

[0009] In another example, the present disclosure provides a pharmaceutical composition comprising a compound provided herein (e.g., a compound of Formula I), or a salt (e.g., a pharmaceutically acceptable salt) thereof, together with a pharmaceutically acceptable carrier.

[0010] In another example, the present disclosure provides a method of inhibiting, disrupting, and/or preventing an interaction between a PI3Kα protein and a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) such that the kinase activity of the PI3Kα protein is not inhibited. In some examples, the PI3Kα protein is in a cell, such as in a cell of a human or animal subject (e.g., as described herein).

[0011] In a further example, the present disclosure provides a method of treating, ameliorating, delaying the progress of, ameliorating or eliminating a symptom of, and/or inhibiting a cancer and/or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K) comprising administering a compound provided herein (e.g., a compound of Formula I), or a salt (e.g., a pharmaceutically acceptable salt) thereof.

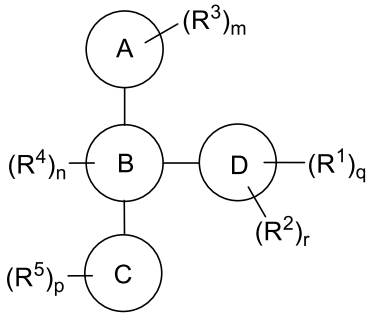
[0012] In a related example, the present disclosure provides a use of a compound provided herein (e.g., a compound of Formula I), or a salt (e.g., a pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for the treatment, amelioration, or inhibition of a cancer or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K). The present disclosure also provides a compound (e.g., a compound of Formula I), or a salt (e.g., a pharmaceutically acceptable salt) thereof, for use as a medicament, which medicament may be used in the treatment, amelioration, or inhibition of a cancer or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K).

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIG. 1** shows the effect of inhibiting PI3Kα with a PI3Kα kinase inhibitor such as alpelisib in normal cells (left panel) and tumor cells (right panel). In normal cells, inhibiting PI3Kα blocks normal cell signaling resulting in dose-limiting hyperglycemia and insulin-driven resistance. The right panel shows an alternative scheme of using a PI3Kα breaker to inhibit the PI3Kα:RAS protein:protein interaction in tumor cells. This mechanism should avoid hyperglycemia and insulin-driven resistance by selectively targeting tumor cells and may provide multiple therapeutic advantages. The observation that mutations in the RAS binding domain that impair the PI3Kα:RAS interaction blocks oncogene-driven non-small cell lung cancer (NSCLC) tumor growth in vivo and have no effect on glucose metabolism support the potential of this mechanism.

CLAIMS

1. A compound of formula I:



I

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

Ring A is selected from phenyl and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is a 9- to 10-membered bicyclic ring that comprises at least one 5- or 6-membered heteroaryl ring;

Ring C is selected from phenyl; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 8-membered bicyclic carbocyclic ring; a 4- to 8-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7- to 10-membered spirofused heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each of the phenyl, heteroaryl, and heterocyclic rings is optionally fused to Ring E;

Ring D is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and phenyl, wherein each of the heteroaryl and phenyl rings is optionally fused to Ring F;

Ring E is selected from a 5- to 6-membered carbocyclic ring; a 5- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 7- to 10-membered spirofused heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring E is substituted by s instances of $R^{5'}$;

Ring F is selected from phenyl; a 5- to 6-membered carbocyclic ring; a 5- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring F is substituted by u instances of –L-W and y instances of $R^{2'}$;

R^1 is selected from –L-W, Ring D′, or a bivalent C_{1-6} aliphatic chain substituted with Ring D′;

each –L-W is –CN, or:

each L is independently a bivalent straight or branched C_{1-8} aliphatic chain wherein one or more methylene units of the aliphatic chain are optionally and independently replaced by a group selected from -N(R)-, -O-, -S-, -C(O)-, -SO_2-, -CH(X)-, -$C(X)_2$-, -C(O)N(R)-, -N(R)C(O)-, -C(O)O-, -OC(O)-, -SO_2N(R)-, and -N(R)SO_2-;

each W is independently hydrogen, halogen, -CN, or an optionally substituted 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each X is independently halogen, -OR, or -CN;

each Ring D′ is independently a 4- to 6-membered carbocyclic ring or a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring D′ is substituted with t instances of –L-W;

each R^2 and $R^{2'}$ is independently selected from oxo, halogen, -CN, -OR, and C_{1-6} alkyl;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -O$(CH_2)_v$Cy, -OCH_2CH_2OR, and optionally substituted C_{1-6} aliphatic;

each Cy is independently a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3- to 6-membered carbocyclic ring; or a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-2 instances of R^6;

each R^4 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each of R^5 and $R^{5'}$ is independently selected from oxo, =NH, -CN, halogen, -OR, -$N(R)_2$, -SR, -C(O)R, -N(R)C(O)R, -$(CH_2)_x$C(O)$N(R)_2$, -C(O)$N(R)_2$, -C(O)N(R)$(CH_2)_x$Cy, -$(CH_2)_x$C(O)Cy, -OC(O)R, -C(O)OR, -SO_2R, -N(R)SO_2R, -N=S(O)$(R)_2$, -$SO_2N(R)_2$, -P(O)R_2, -$(CH_2)_x$Cy, -O$(CH_2)_x$Cy, and optionally substituted C_{1-6} aliphatic;

each R^6 is independently selected from oxo, -CN, halogen, -OR, -$N(R)_2$, -SR, -C(O)R, -N(R)C(O)R, -C(O)$N(R)_2$, -OC(O)R, -C(O)OR, -SO_2R, -N(R)SO_2R, -$SO_2N(R)_2$, and an optionally substituted group selected from C_{1-6} aliphatic; a 3- to 6-membered carbocyclic ring; phenyl; a 3- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 10-membered aryl ring; and a 9- to 10-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic; a 3- to 6-membered carbocyclic ring; phenyl; a 3- to 6-membered

heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 10-membered aryl ring; and a 9- to 10-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0 or 1;

r is 0, 1, or 2;

s is 0, 1, 2, or 3;

t is 0, 1, or 2;

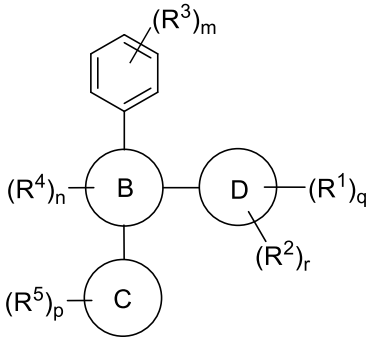
u is 0 or 1;

each v is independently 0, 1, or 2;

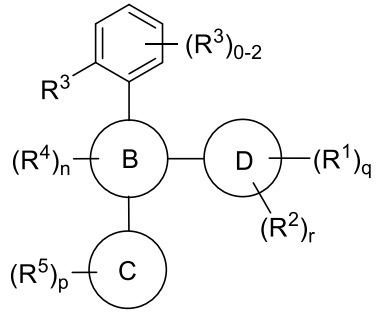
each x is independently 0, 1, or 2; and

y is 0, 1, or 2.

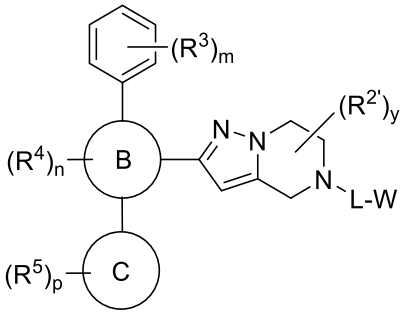
2. The compound of claim 1, wherein the compound is a compound according to any one of Formulae IA, IA1, IC, IC1, IE, and IE1:



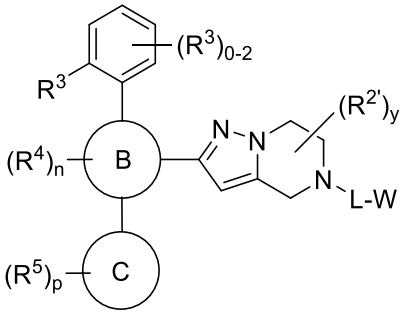
IA



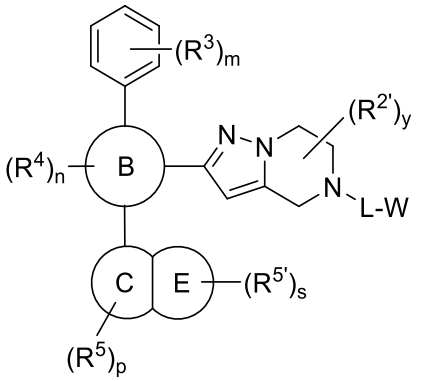
IA1



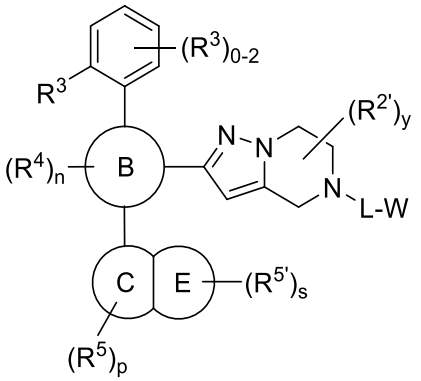
IC



IC1



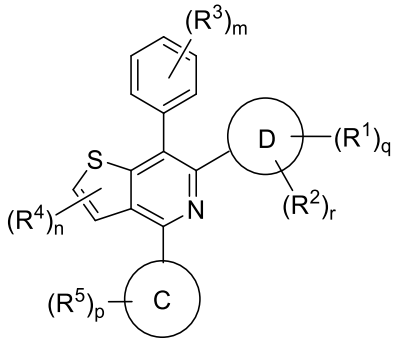
IE



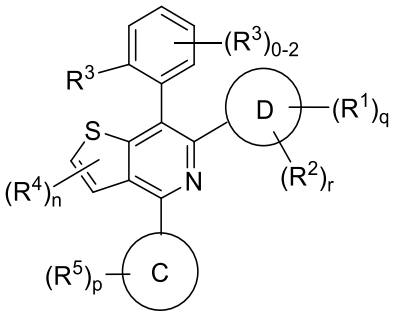
IE1

or a salt (e.g., pharmaceutically acceptable salt) thereof.

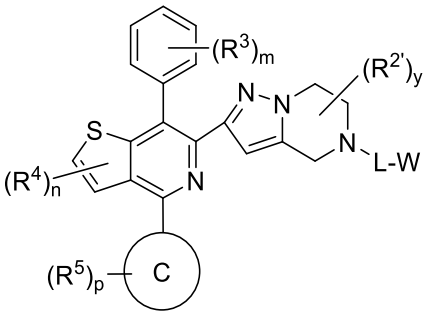
3. The compound of claim 1, wherein the compound is a compound according to any one of Formulae IB, IB1, ID, ID1, IF, and IF1:



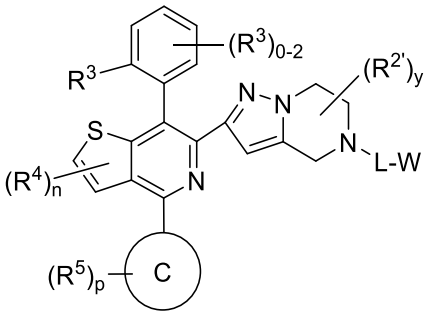
IB



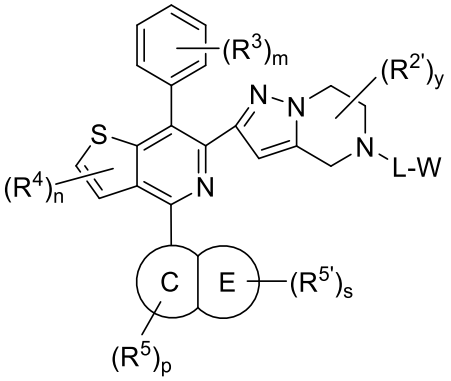
IB1

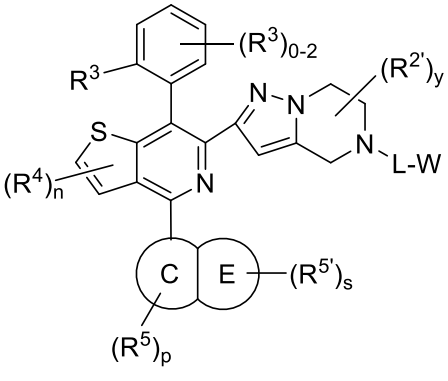


ID



ID1

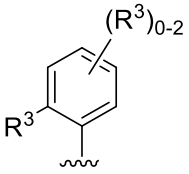


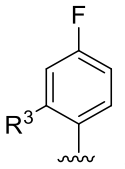
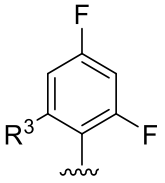


IF **IF1**

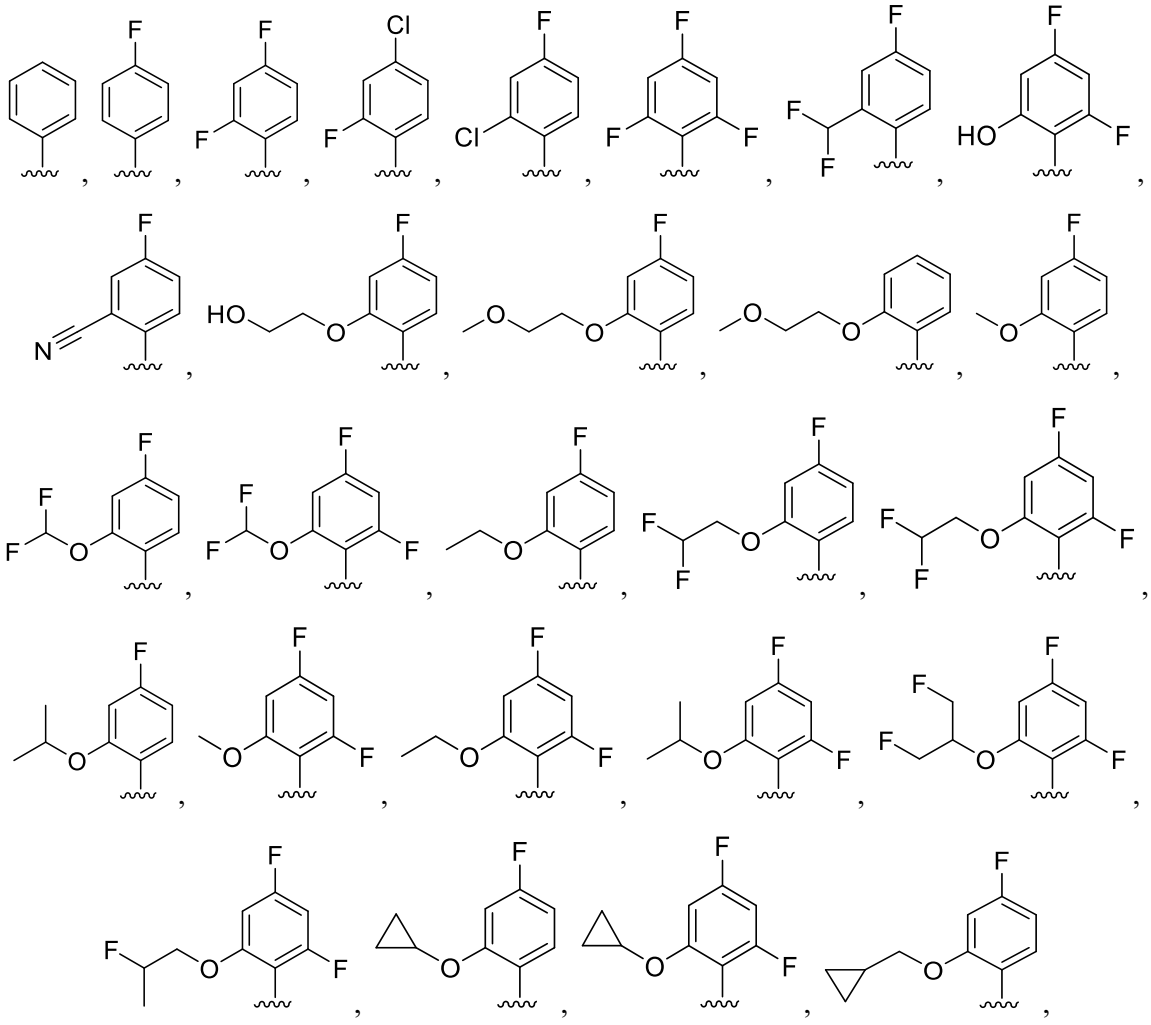
or a salt (e.g., pharmaceutically acceptable salt) thereof.

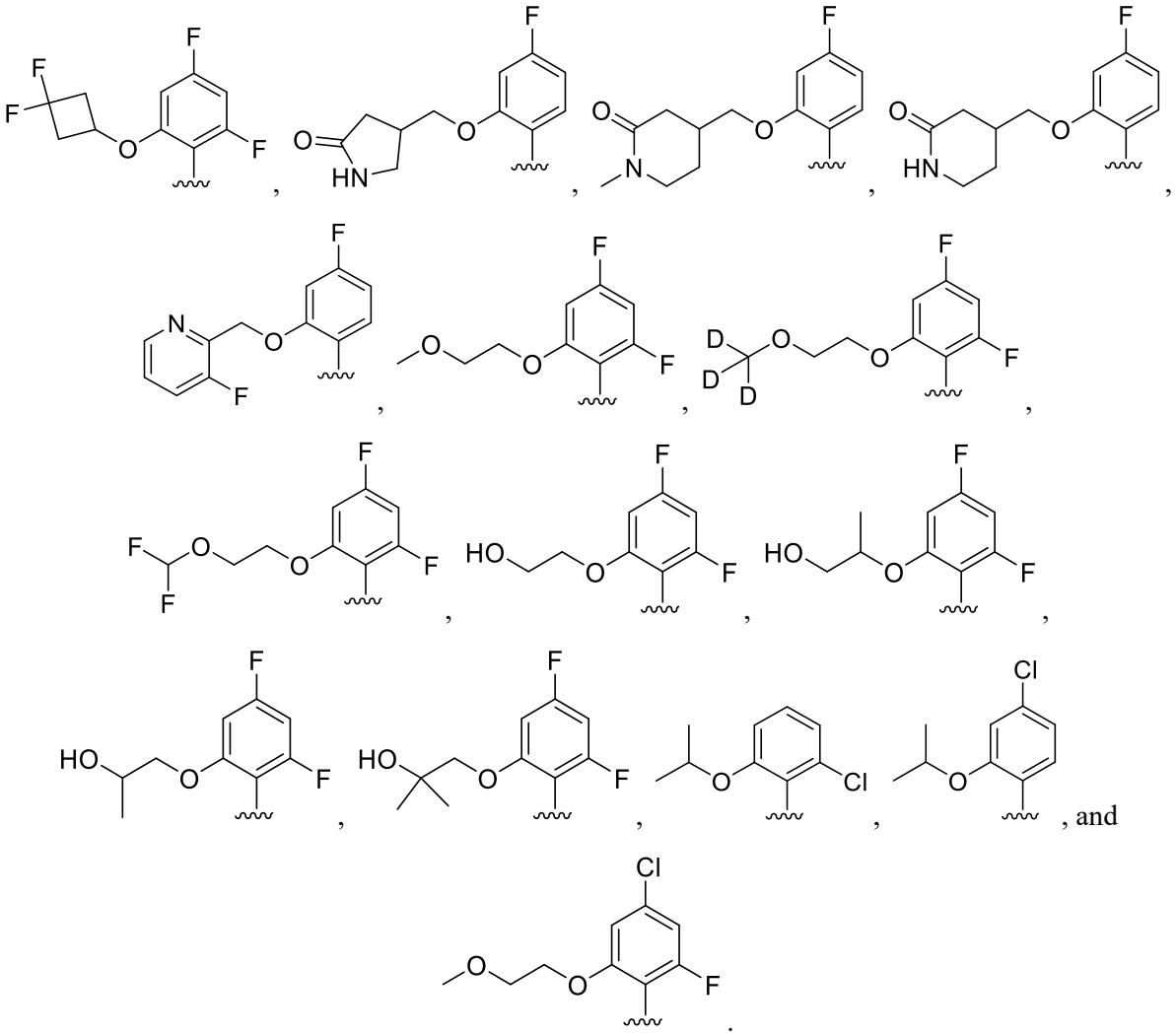
4. The compound of claim 1, wherein Ring A is phenyl.

5. The compound of claim 4, wherein Ring A is  .

6. The compound of claim 5, wherein Ring A is selected from  and  .

7. The compound of any one of claims 4-6, wherein Ring A, substituted with m instances of R^3, is selected from





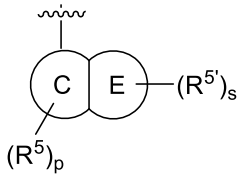
8. The compound of any one of claims 1-7, wherein m is 1, 2, or 3.

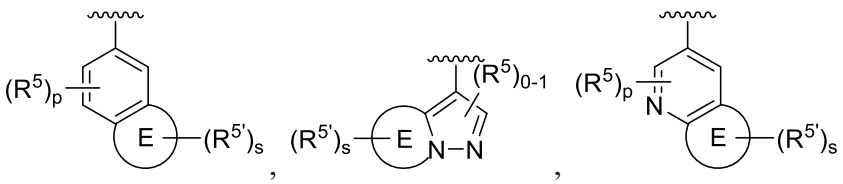
9. The compound of any one of claims 1-8, wherein at least one R^3 is selected from halogen, -OR, $-O(CH_2)_vCy$, and -O-(C_{1-4} alkylene)-OR.

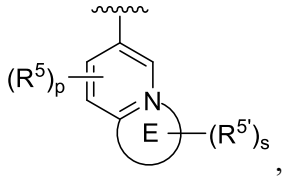
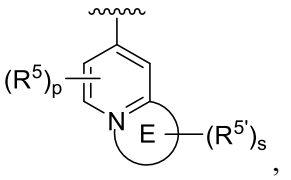
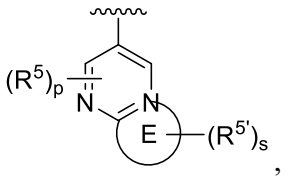
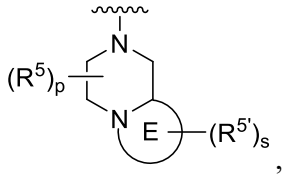
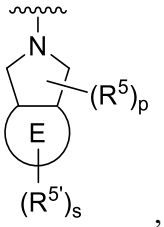
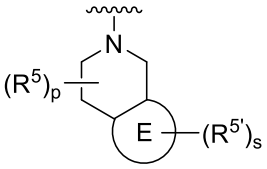
10. The compound of any one of claims 1-9, wherein each R^4 is halogen.

11. The compound of any one of claims 1-10, wherein Ring C is phenyl.

12. The compound of any one of claims 1-11, wherein Ring C is fused to Ring E.

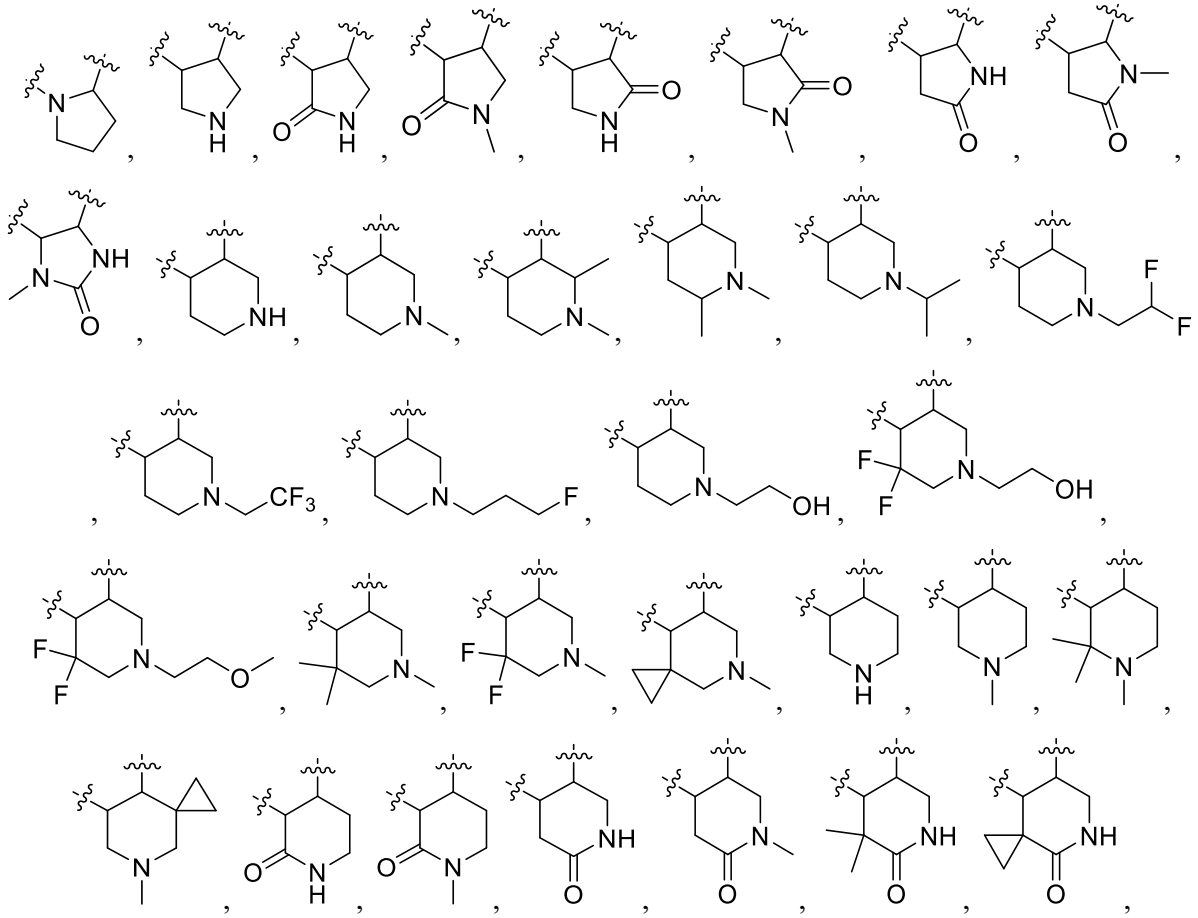
13. The compound of claim 12, wherein  is selected from

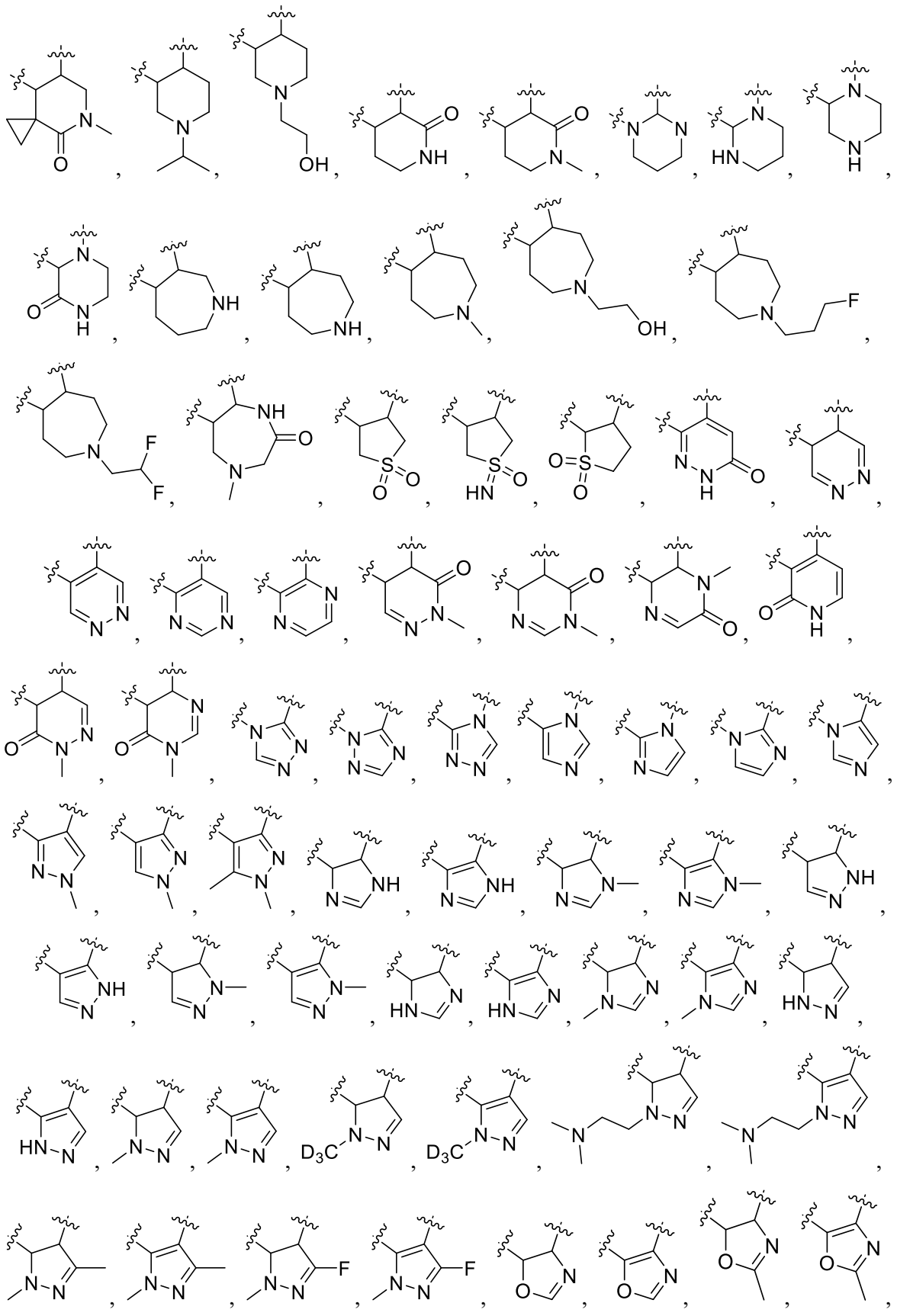


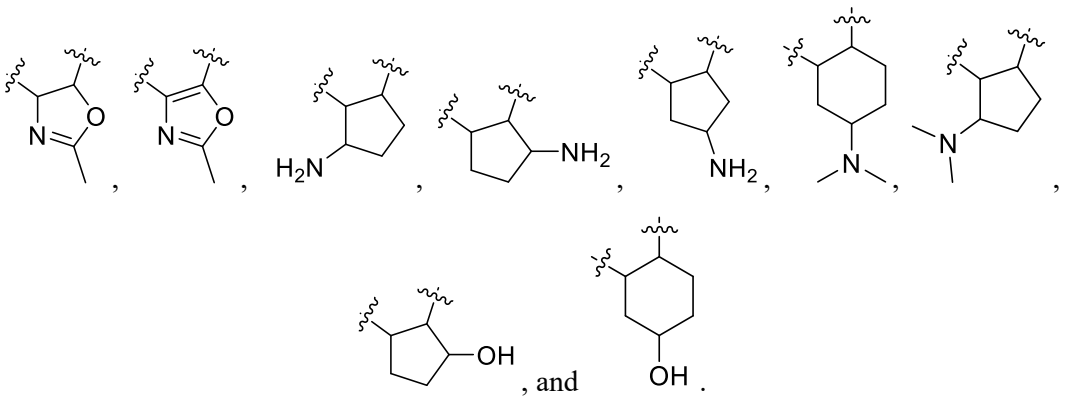





, and

.

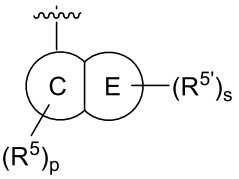
14. The compound of claim 12 or 13, wherein Ring E is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring E is substituted by s instances of $R^{5'}$.

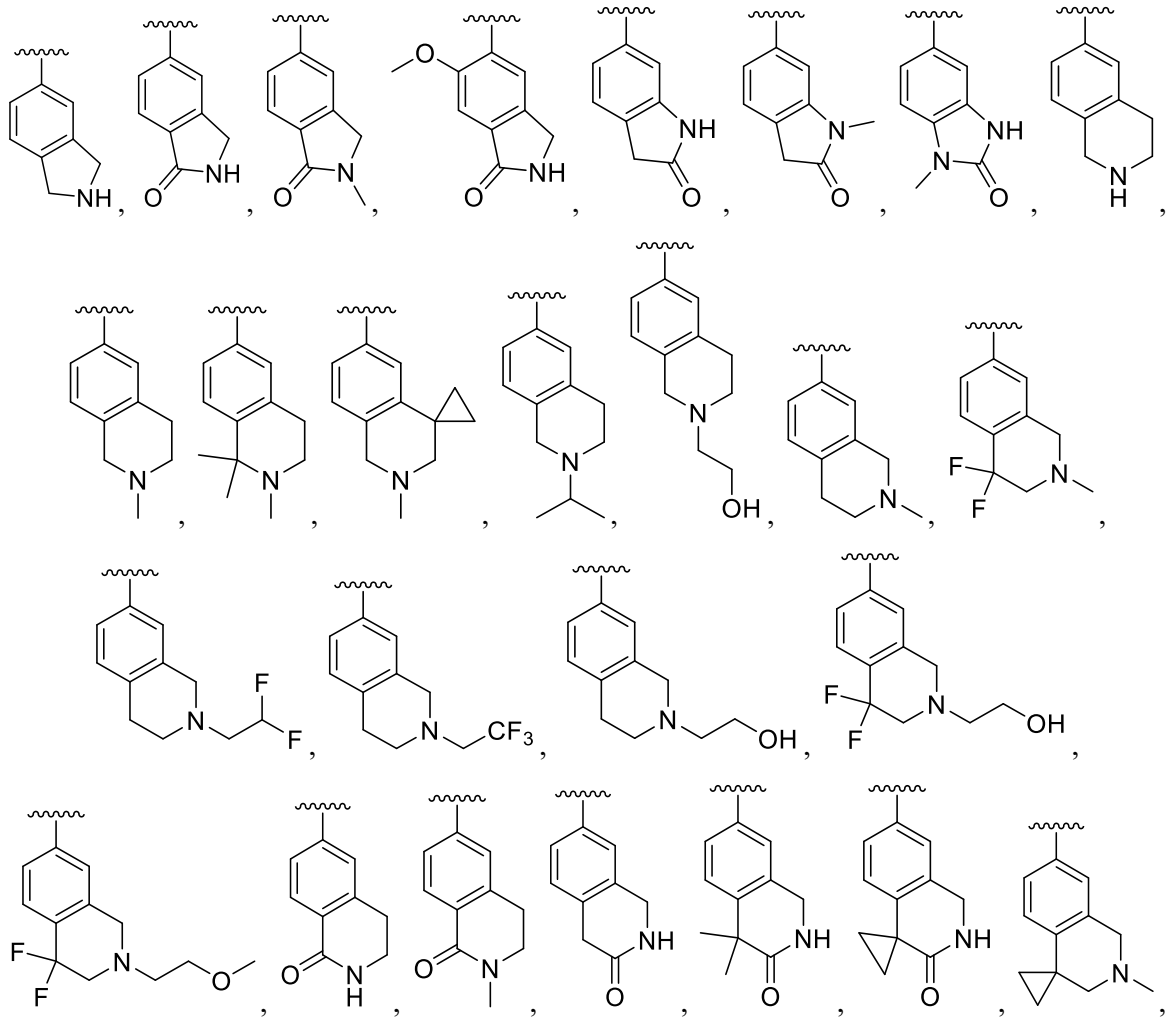
15. The compound of any one of claims 12-14, wherein Ring C is fused to Ring E, and Ring E, substituted with s instances of $R^{5'}$, is selected from:

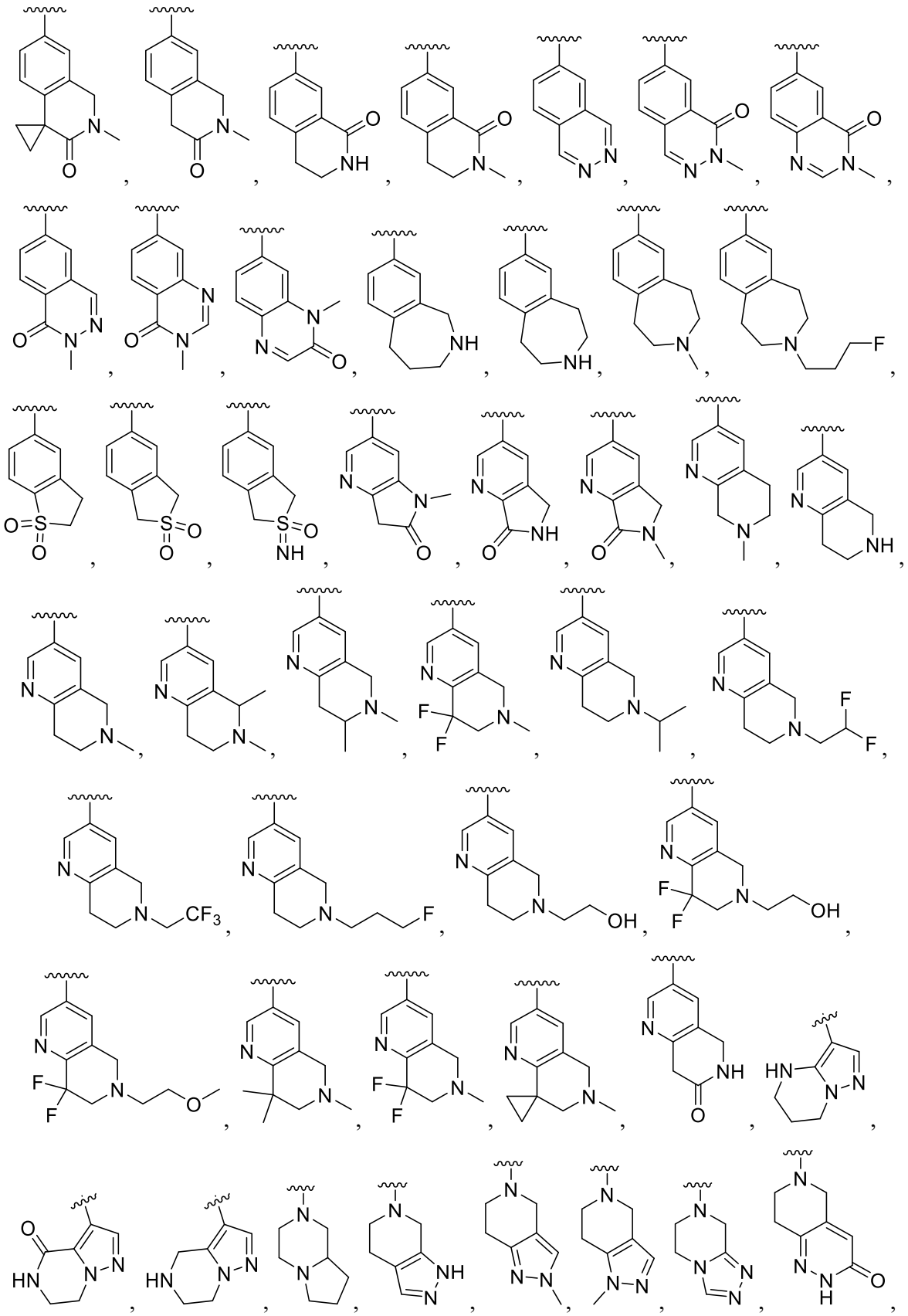


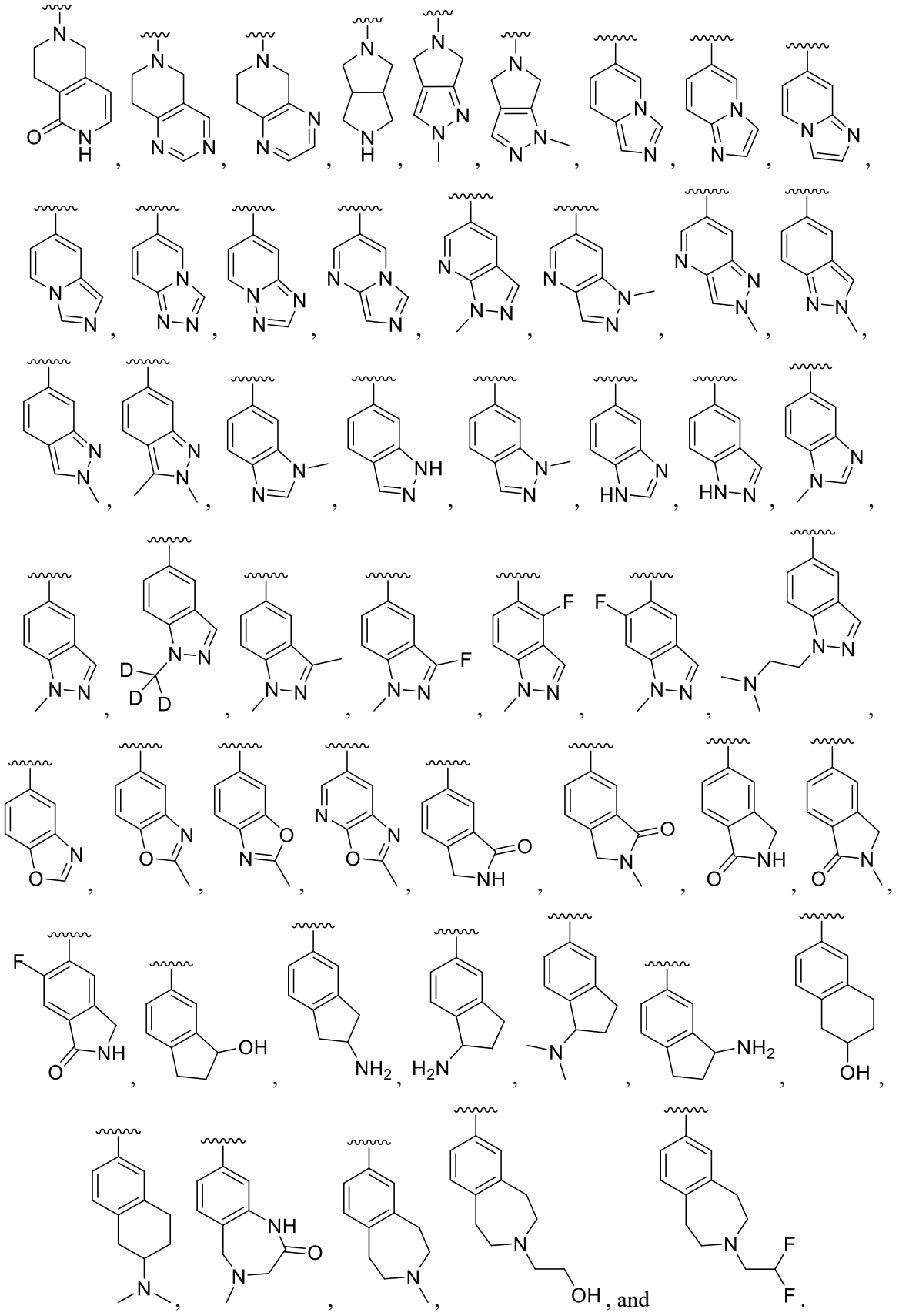




16. The compound of any one of claims 12-15, wherein  is selected from:







17. The compound of any one of claims 1-16, wherein p is 0.

18. The compound of any one of claims 1-17, wherein each $R^{5'}$ is independently selected from oxo, =NH, -CN, halogen, -OR, -$N(R)_2$, -SR, -C(O)R, -N(R)C(O)R, -$(CH_2)_xC(O)N(R)_2$, -

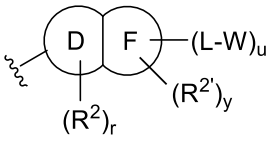
$(CH_2)_xC(O)Cy$, -OC(O)R, -C(O)OR, $-SO_2R$, $-N(R)SO_2R$, $-N{=}S(O)(R)_2$, $-SO_2N(R)_2$, $-P(O)(R)_2$, $-(CH_2)_xCy$, $-O(CH_2)_xCy$, and C_{1-6} aliphatic, wherein C_{1-6} aliphatic is unsubstituted or substituted with one or more halogen, -CN, $-N(R)C(O)R$, $-N(R)_2$, or –OR.

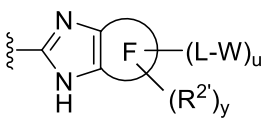
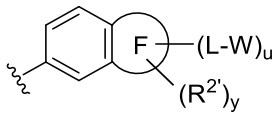
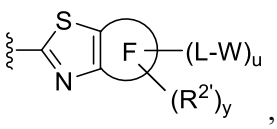
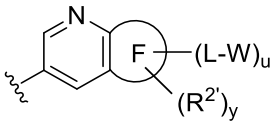
19. The compound of any one of claims 1-18, wherein s is 1 or 2.

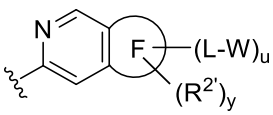
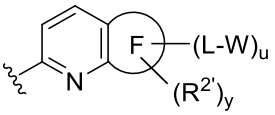
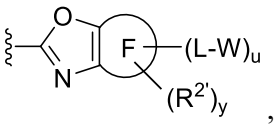
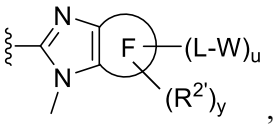
20. The compound of any one of claims 1-19, wherein Ring D is a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

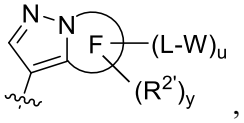
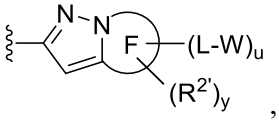
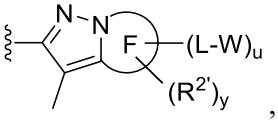
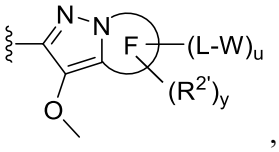
21. The compound of any one of claims 1-20, wherein Ring D is fused to Ring F.

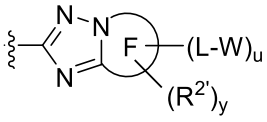
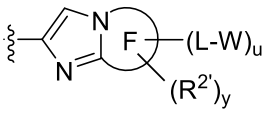
22. The compound of claim 21, wherein q is 0.

23. The compound of claim 22, wherein  is selected from:

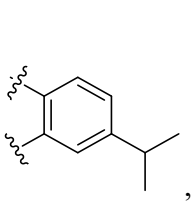
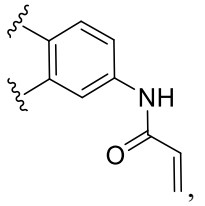
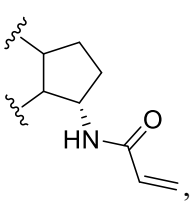
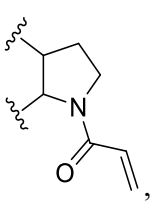
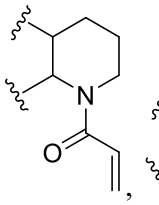
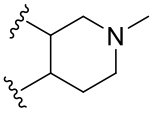
 ,  ,  ,  ,

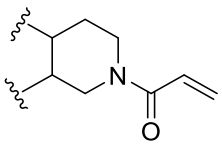
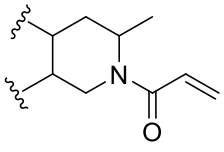
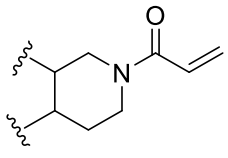
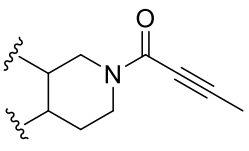
 ,  ,  ,  ,

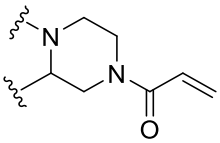
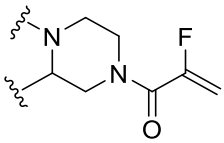
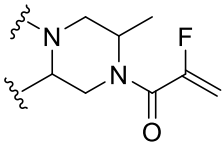
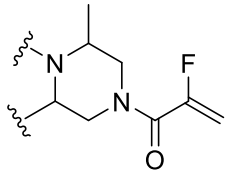
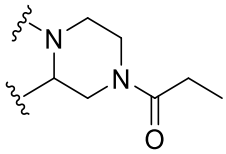
 ,  ,  ,  ,

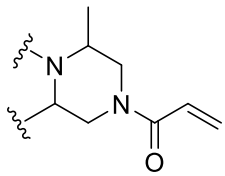
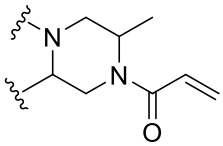
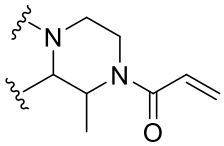
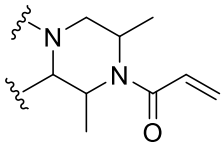
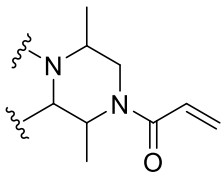
 , and  .

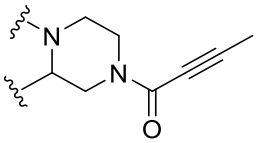
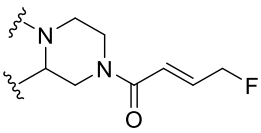
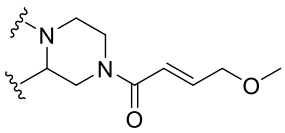
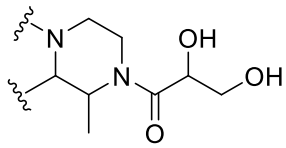
24. The compound of claim 22 or 23, wherein Ring F, substituted with u instances of -L-W and y instances of $R^{2'}$, is selected from:

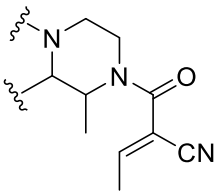
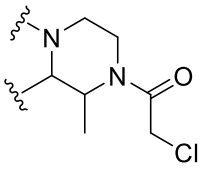
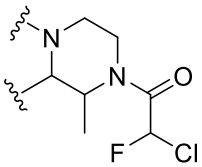
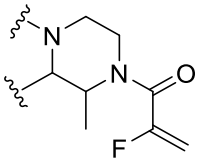
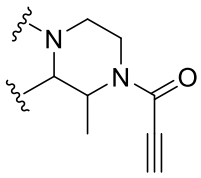
 ,  ,  ,  ,  ,  ,

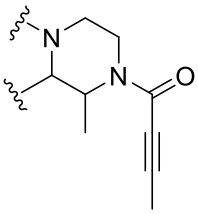
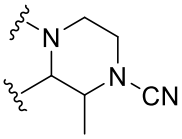
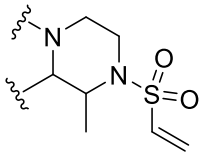
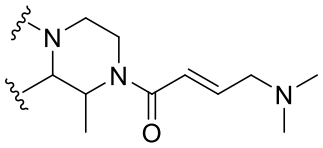
 ,  ,  ,  ,

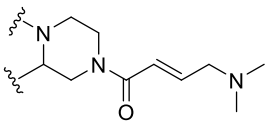
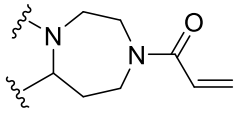
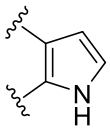
 ,  ,  ,  ,  ,

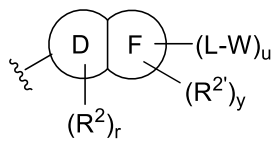
 ,  ,  ,  ,  ,

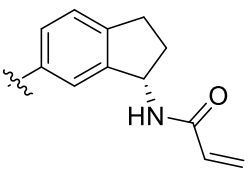
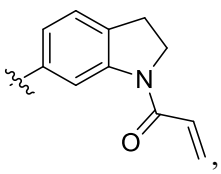
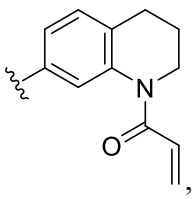
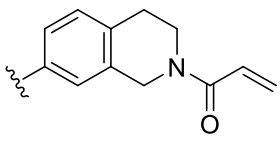
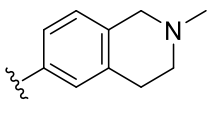
 ,  ,  ,  ,

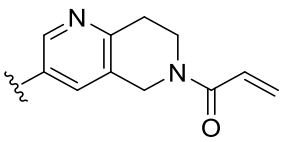
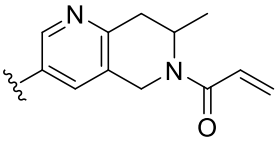
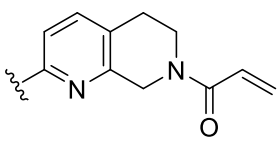
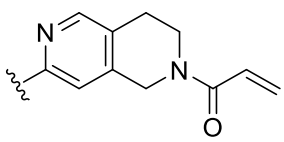
 ,  ,  ,  ,  ,

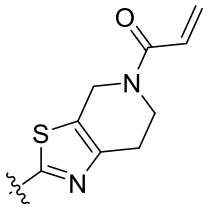
 ,  ,  ,  ,

 ,  , and  .

25. The compound of any one of claims 21-24, wherein  is selected from:

 ,  ,  ,  ,  ,

 ,  ,  ,  ,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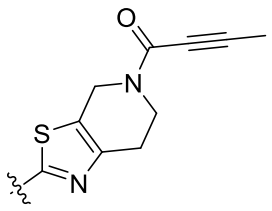
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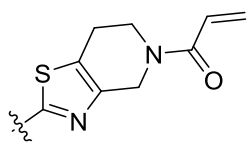
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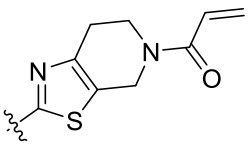
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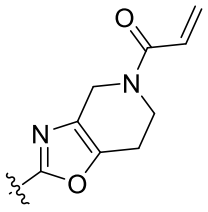
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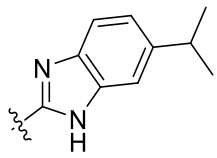
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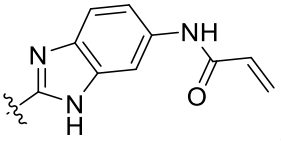
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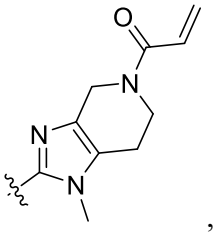
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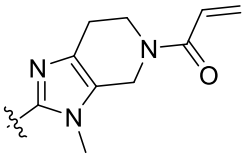
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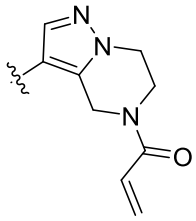
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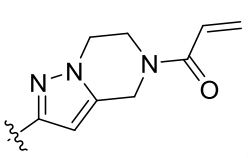
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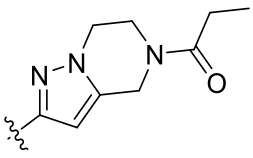
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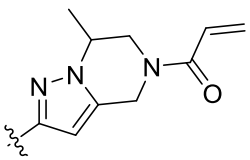
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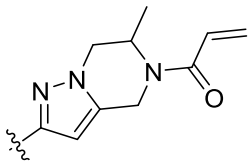
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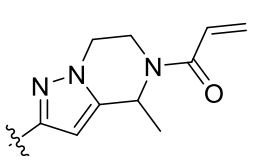
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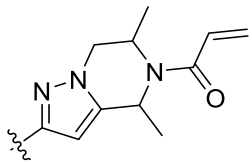
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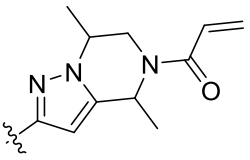
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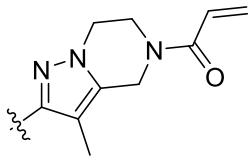
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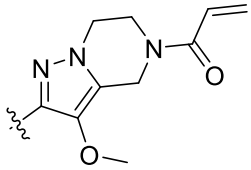
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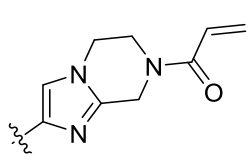
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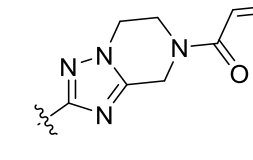
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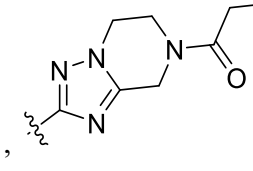
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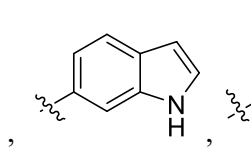
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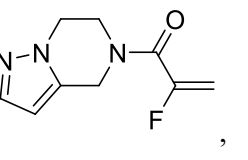
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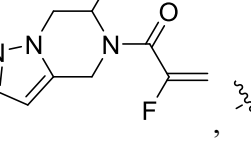
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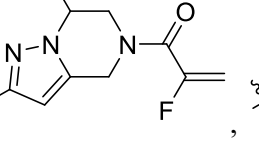
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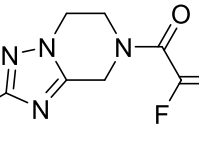
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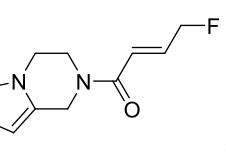
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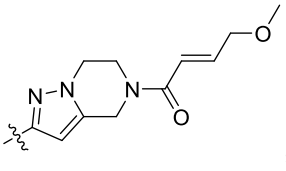
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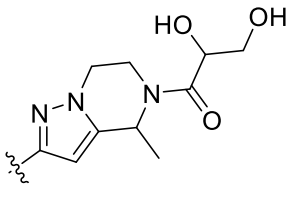
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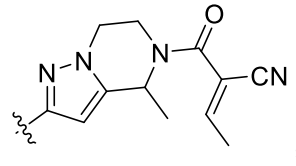
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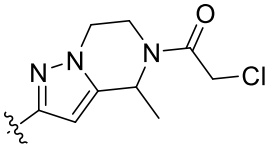
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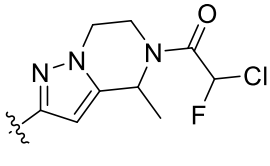
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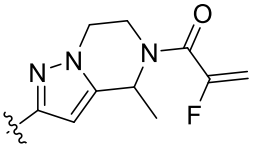
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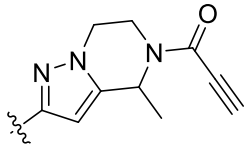
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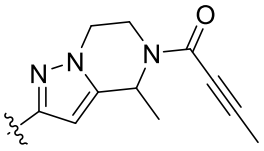
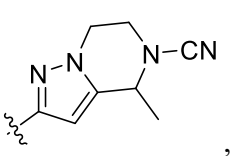
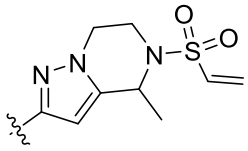
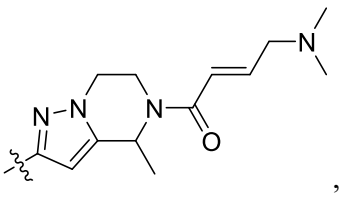
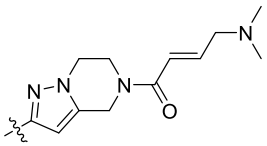
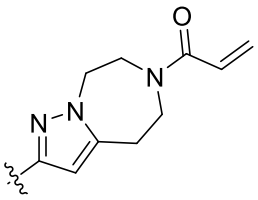
 ,  ,  ,  ,  , and  .

26. The compound of any one of claims 21-25, wherein u is 1.

27. The compound of any one of claims 21-26, wherein each $R^{2'}$ is independently selected from C_{1-6} alkyl.

28. The compound of any one of claims 21-27, wherein y is 1 or 2.

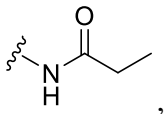
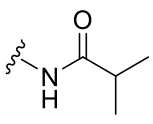
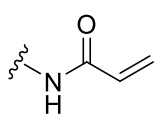
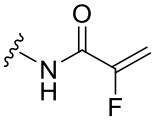
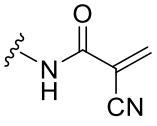
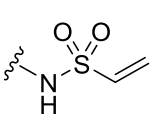
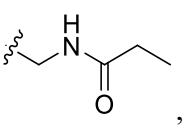
29. The compound of any one of claims 1-28, wherein r is 0.

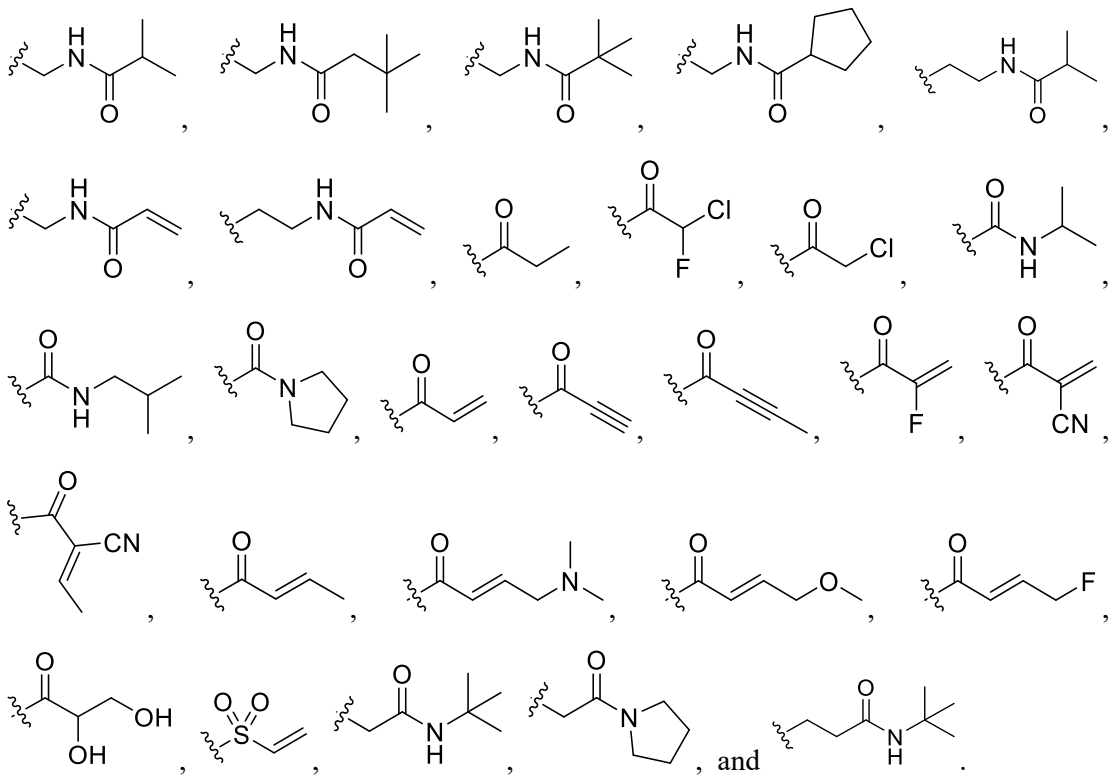
30. The compound of any one of claims 1-29, wherein each L is independently selected from a bivalent straight or branched C_{1-8} aliphatic chain having one or more units of unsaturation, wherein one or more methylene units of the aliphatic chain are optionally and independently replaced by a group selected from -N(R)-, -O-, -S-, -C(O)-, $-SO_2-$, -CH(X)-, $-C(X)_2-$, -C(O)N(R)-, -N(R)C(O)-, -C(O)O-, -OC(O)-, $-SO_2N(R)-$, and $-N(R)SO_2-$.

31. The compound of any one of claims 1-30, wherein each L is independently selected from a bivalent straight or branched C_{1-4} aliphatic chain having one double bond, wherein one or two methylene units of the aliphatic chain are optionally and independently replaced by a group selected from -N(R)-, -C(O)-, and -N(R)C(O)-.

32. The compound of any one of claims 1-31, wherein each L is independently selected from -C(O)CClF-, -C(O)CH=CH-, -N(R)C(O)CH=CH-, $-C(O)C(=CH_2)-$, $-C(O)CH=CH-CH_2-$, $-C(O)CH=CHCH_2OCH_2-$, $-C(O)CH=CHCH_2N(R)-$, $-CH_2N(R)C(O)CH=CH-$, and $-CH_2CH_2N(R)C(O)CH=CH-$.

33. The compound of any one of claims 1-32, wherein each W is hydrogen.

34. The compound of any one of claims 1-33, wherein each –L-W is independently selected from $-CH_3$, $-CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2OH$, $-CH_2NH_2$, $-OCH(CH_3)_2$, -CN,  ,  ,  ,  ,  ,  ,  ,



, and .

35. The compound of any one of claims 1-34, wherein each –L-W is independently selected from -C(O)CH=CH_2, -C(O)CF=CH_2, –NHC(O)CF=CH_2, and –NHC(O)CH=CH_2.

36. The compound according to any one of claims 1-35, wherein each R is independently hydrogen, C_{1-6} aliphatic, or C_{1-6} haloaliphatic.

37. A compound selected from Table 1, or a salt (e.g., pharmaceutically acceptable salt) thereof.

38. A compound selected from Table 2, or a salt (e.g., pharmaceutically acceptable salt) thereof.

39. A pharmaceutical composition comprising a compound according to any one of claims 1-38, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable carrier or excipient.

40. Use of a compound according to any one of claims 1-38 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease, disorder, or condition.

41. The use of claim 40, wherein the disease, disorder, or condition is ameliorated by disruption, inhibition, and/or prevention of an interaction between a small GTPase and a PI3Kα protein.

42. The use according to claim 41, wherein the small GTPase is a RAS protein selected from KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, and RIT1.

43. The use according to claim 41, wherein the disease, disorder, or condition is a cancer.

44. The use of claim 43, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

45. The use of claim 44, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

46. The use of any one of claims 43-45, wherein the cancer is characterized by a mutation in a RAS protein.

47. The use of claim 46, wherein the RAS protein is KRAS.

48. The use of claim 47, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

49. The use of claim 48, wherein the KRAS protein comprises a G12C or G12D mutation.

50. The use of claim 43, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases) and/or a mutation in or a deletion of a PTEN protein.

51. The use of any one of claims 43-50, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, bone, connective tissue, skin, cervix, uterus, corpus endometrium, testis, bladder, kidney and other urinary tissues, including renal cell carcinoma (RCC); cancers of the eye, brain, spinal cord, and other components of the central and peripheral nervous systems, as well as associated structures such as the meninges; cancers of the thyroid and other endocrine glands; Hodgkin's disease; non-Hodgkin's lymphomas; multiple myeloma; and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia (CLL), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Acute Myelogenous Leukemia (AML),) and lymphomas including lymphocytic, granulocytic and monocytic lymphomas.

52. The use according to any one of claims 40-42, wherein the subject has a metabolic disorder, a RASopathy, or a vascular disorder.

53. The use according to claim 51, wherein: (i) the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes; (ii) the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome; and/or (iii) the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); or fibro-adipose vascular anomaly (FAVA)).

54. Use of a compound according to any one of claims 1-38, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein, wherein the medicament is to be contacted with a cell containing the small GTPase and the PI3Kα protein.

55. Use of a compound according to any one of claims 1-38, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for contacting a cell containing a small GTPase and a PI3Kα protein.

56. A compound according to any one of claims 1-38, or a pharmaceutically acceptable salt thereof, for use in therapy.