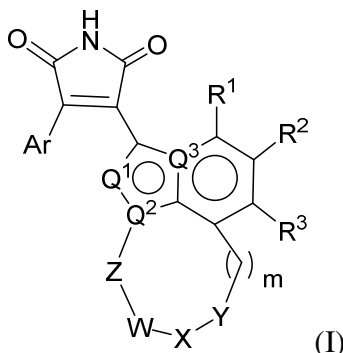


SUMMARY

[0008] The present disclosure provides compounds of Formula (I),



and pharmaceutically acceptable salts and tautomers thereof, wherein:

Q^1 is CH or N;

Q^2 is C or N;

Q^3 is C or N;

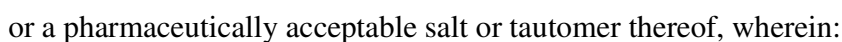
wherein at least one of Q^1 , Q^2 , and Q^3 is N;

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{1a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C_1 - C_4 alkyl;

R^2 is selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NH(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)₂, -NHC(O) R^{2a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C_1 - C_4 alkyl;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C_1 - C_4 alkyl;

[0008a] In one aspect, the present disclosure refers to a compound of Formula (I):



Q^3 is C or N:

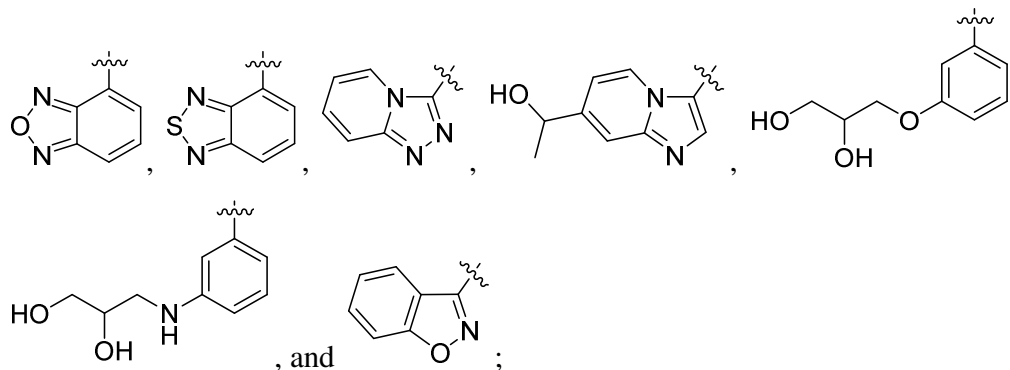
wherein at least one of Q^1 , Q^2 , and Q^3 is N;

R¹ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{1a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C₁-C₄alkyl;

R² is selected from the group consisting of halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NH(C₁-C₄alkyl), -N(C₁-C₄alkyl)₂, -NHC(O)R^{2a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C₁-C₄alkyl;

R³ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{3a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C₁-C₄alkyl;

Chemical structures of indazole, benzoxazole, and benzothiazole are shown, separated by commas. Each structure has a wavy line indicating a point of attachment.


$$-Z-W-X-Y- \text{ is } -C(R^Z)_2-C(R^W)_2-N(R^X)-C(R^Y)_2-, -C(R^Z)_2-C(R^W)_2-CH(R^X)-C(R^Y)_2-,$$

each R^Z is independently selected from the group consisting of hydrogen, deuterium,

each R^W is independently selected from the group consisting of hydrogen, deuterium,

or R^Z and R^W together with the carbons to which they are attached form a C_3 -

R^X is selected from the group consisting of -COR^{X1}, -SO₂R^{X1}, heteroaryl, and -(C₁-

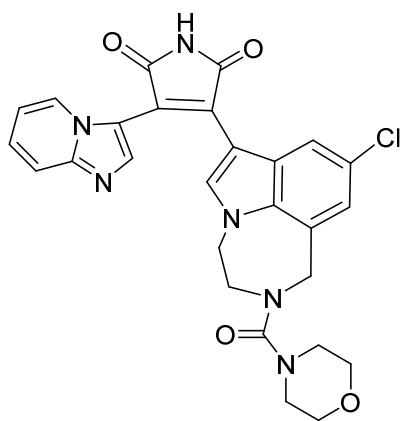
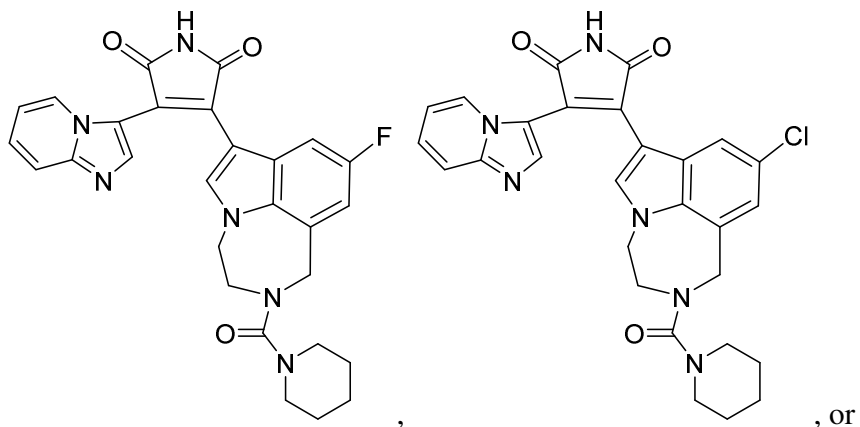
wherein R^{X1} is heterocyclyl, wherein the heterocyclyl is optionally substituted with one

or R^{X1} is $N(R^{X2})$, wherein R^{X2} is independently selected from hydrogen, alkyl, substituted

each R^Y is independently selected from the group consisting of hydrogen, deuterium,

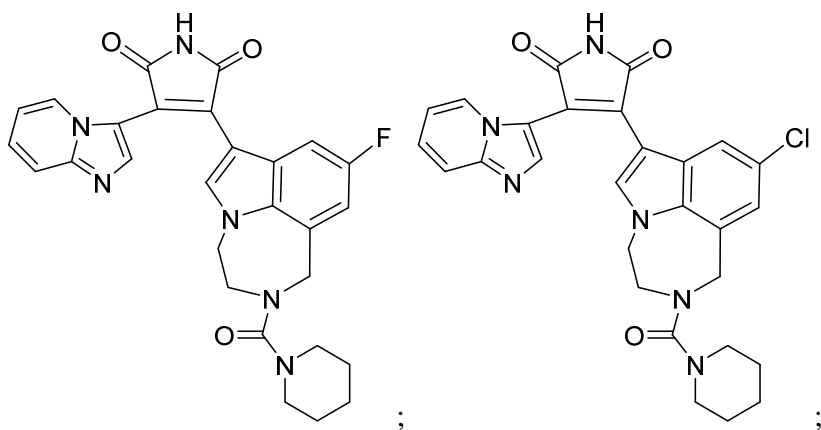
m is 0, 1, or 2;

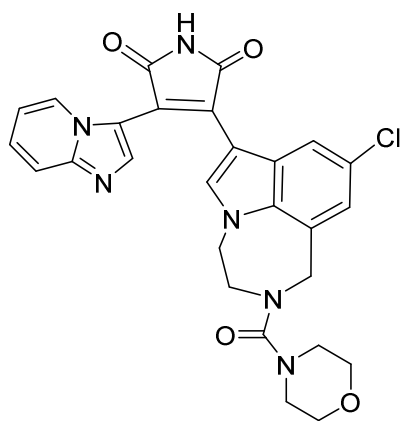
provided that the compound is not



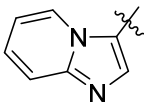
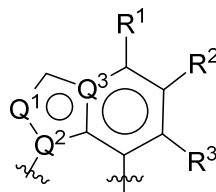
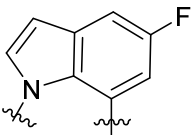
[0009] In some examples, the compounds of Formula (I) have one or more of the following features:

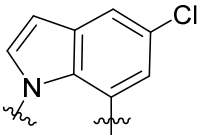
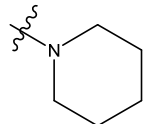
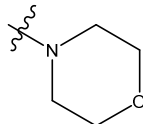
a) provided that the compound is not





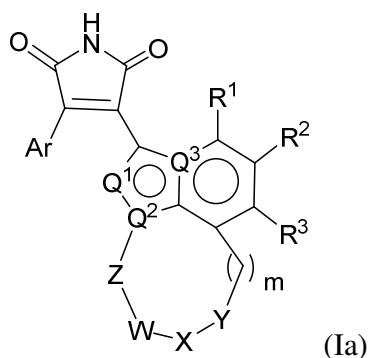
or ;

b) provided that when Ar is , and , is  or

 then R^{X1} is not  nor  ;

[0010] The present disclosure provides compounds of Formula (Ia):

[0010a] In another aspect, the present disclosure refers to a compound of Formula (Ia):



or a pharmaceutically acceptable salt or tautomer thereof, wherein:

Q^1 is CH or N;

Q^2 is C or N;

Q^3 is C or N;

wherein at least one of Q^1 , Q^2 , and Q^3 is N;

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C_1 - C_4 alkyl;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NH(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)₂, -NHC(O) R^{2a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C_1 - C_4 alkyl;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C_1 - C_4 alkyl;

Chemical structures of three benzimidazole derivatives are shown, separated by commas. Each structure has a wavy line at the 4-position indicating a substituent.

- Structure 1: 2-oxo-1,2,3,4-tetrahydro-1H-benzimidazole (a benzimidazole with an oxygen atom at position 2).
- Structure 2: 2,3-dithia-1,2,3,4-tetrahydro-1H-benzimidazole (a benzimidazole with sulfur atoms at positions 2 and 3).
- Structure 3: 2,3-dihydro-1H-benzimidazole (a benzimidazole with a double bond between positions 2 and 3).

[illegible]

Q⁷ is selected from S, O, CH₂, and NR^{Q7}; wherein R^{Q7} is hydrogen or optionally substituted C₁-C₄alkyl;

-Z-W-X-Y- is -C(R^Z)₂-C(R^W)₂-N(R^X)-C(R^Y)₂-, -C(R^Z)₂-C(R^W)₂-CH(R^X)-C(R^Y)₂-,
or -C(R^W)₂-CH(R^X)-C(R^Y)₂-;

each R^Z is independently selected from the group consisting of hydrogen, deuterium, halo, and C₁-C₄alkyl, or both R^Z groups together form C₃-C₆cycloalkyl or oxo;

each R^W is independently selected from the group consisting of hydrogen, deuterium, halo, and C₁-C₄alkyl, or both R^W groups together form C₃-C₆cycloalkyl or oxo;

or R^Z and R^W together with the carbons to which they are attached form a C₃-C₆cycloalkyl;

R^X is selected from the group consisting of hydrogen, R^{X1}, -COR^{X1}, -SO₂R^{X1}, -(C₁-C₄alkylene)-R^{X1}, and wherein the -(C₁-C₄alkylene)-R^{X1} is optionally substituted with one to four halo on the C₁-C₄alkylene;

wherein R^{X1} is C₃-C₈cycloalkyl, heteroaryl, or heterocyclyl, wherein the heterocyclyl is optionally substituted with one to twelve substituents independently selected from the group consisting of deuterium, halo, -[C(R^{X1a})₂]_p-CN, -CF₃, C₁-C₄alkyl, -(CH₂)_p-OH, -[C(R^{X1a})₂]_p-OH, -[C(R^{X1a})₂]_p-O-C₁-C₄alkyl, -NHCOC₁-C₄alkyl, CONHC₁-C₄alkyl, COH, -CO₂H, -[C(R^{X1a})₂]_p-COO-C₁-C₄alkyl, -(CH₂)_p-NH₂, -[C(R^{X1a})₂]_p-NH₂, -[C(R^{X1a})₂]_p-NH-C₁-C₄alkyl, -[C(R^{X1a})₂]_p-N-(C₁-C₄alkyl)₂; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, -CF₃, and C₁-C₄alkyl, or both R^{X1a} groups together form C₃-C₆cycloalkyl;

or R^{X1} is $N(R^{X2})_2$ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted alkyl, wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

each R^Y is independently selected from the group consisting of hydrogen, deuterium, halo, and C₁-C₄alkyl, or both R^Y groups together form C₃-C₆cycloalkyl or oxo; and m is 0, 1, or 2.

[0011] The present disclosure provides compounds of Formula (Ib):

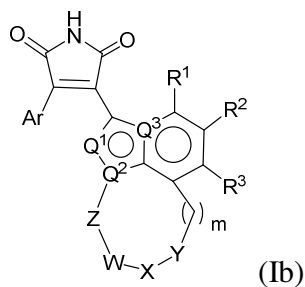
-[C(R^{X1a})₂]_p-O-C₁-C₄alkyl, -NHCOC₁-C₄alkyl, CONHC₁-C₄alkyl, COH, -CO₂H, -[C(R^{X1a})₂]_p-COO-C₁-C₄alkyl, -(CH₂)_p-NH₂, -[C(R^{X1a})₂]_p-NH₂, -[C(R^{X1a})₂]_p-NH-C₁-C₄alkyl, -[C(R^{X1a})₂]_p-N-(C₁-C₄alkyl)₂; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, -CF₃, and C₁-C₄alkyl, or both R^{X1a} groups together form C₃-C₆cycloalkyl;

or R^{X1} is N(R^{X2})₂ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted alkyl, wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

each R^Y is independently selected from the group consisting of hydrogen, deuterium, halo, and C₁-C₄alkyl, or both R^Y groups together form C₃-C₆cycloalkyl or oxo; and

m is 0, 1, or 2.

[0011a] In another aspect, the present disclosure refers to a compound of Formula (Ib):



or a pharmaceutically acceptable salt or tautomer thereof, wherein:

Q¹ is CH or N;

Q² is C or N;

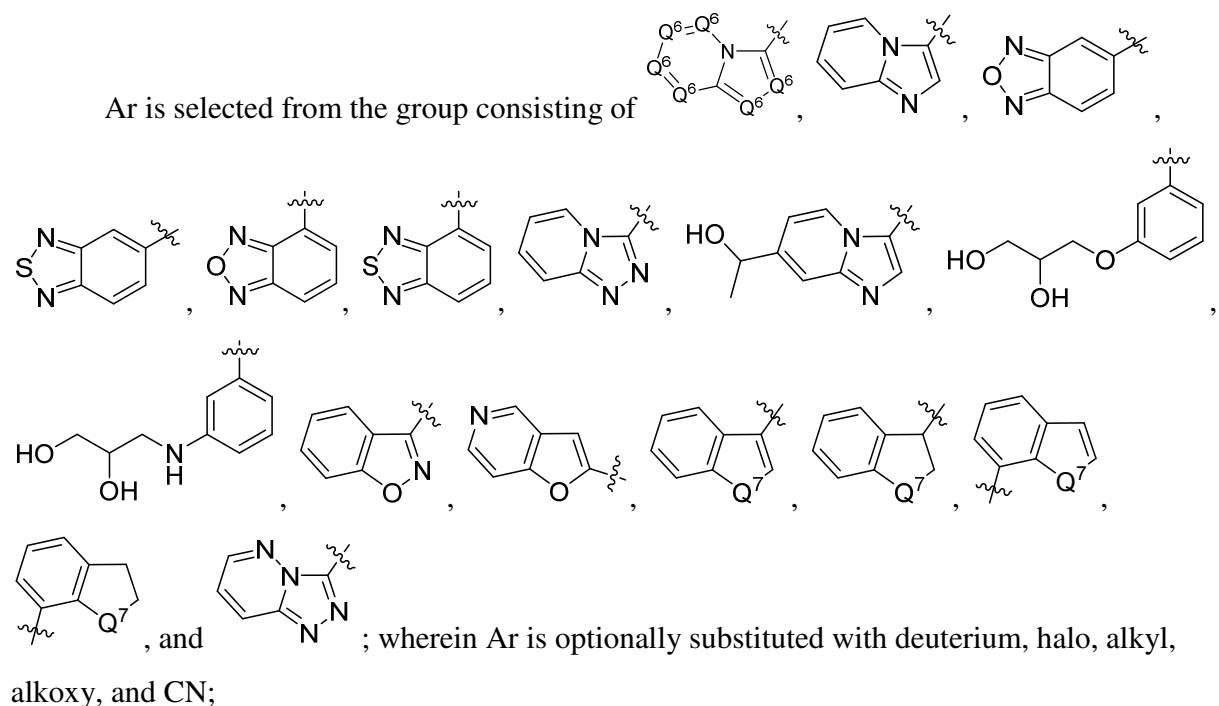
Q³ is C or N;

wherein at least one of Q¹, Q², and Q³ is N; and provided that when Q¹ is CH and Q³ is C, Q² is not N;

R¹ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{3a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C₁-C₄alkyl;

R² is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NH(C₁-C₄alkyl), -N(C₁-C₄alkyl)₂, -NHC(O)R^{2a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C₁-C₄alkyl;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C_1 - C_4 alkyl;

Ar is selected from the group consisting of ; wherein Ar is optionally substituted with deuterium, halo, alkyl, alkoxy, and CN;

each Q^6 is independently selected from CR^{Q6} and N; wherein CR^{Q6} is hydrogen, halo, -CN, lower alkyl, or substituted alkyl;

Q^7 is selected from S, O, CH₂, and NR^{Q7} ; wherein R^{Q7} is hydrogen or optionally substituted C_1 - C_4 alkyl;

-Z-W-X-Y- is $-C(R^Z)_2-C(R^W)_2-N(R^X)-C(R^Y)_2-$, $-C(R^Z)_2-C(R^W)_2-CH(R^X)-C(R^Y)_2-$, or $-C(R^W)_2-CH(R^X)-C(R^Y)_2-$;

each R^Z is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^Z groups together form C_3 - C_6 cycloalkyl or oxo;

each R^W is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^W groups together form C_3 - C_6 cycloalkyl or oxo;

or R^Z and R^W together with the carbons to which they are attached form a C_3 - C_6 cycloalkyl;

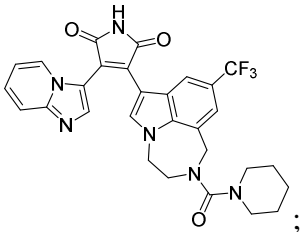
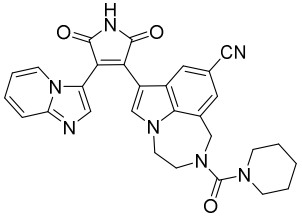
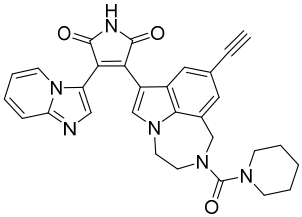
R^X is selected from the group consisting of hydrogen, R^{X1} , $-\text{COR}^{X1}$, $-\text{SO}_2\text{R}^{X1}$, $-(\text{C}_1\text{-C}_4\text{alkylene})\text{-R}^{X1}$, and wherein the $-(\text{C}_1\text{-C}_4\text{alkylene})\text{-R}^{X1}$ is optionally substituted with one to four halo on the $\text{C}_1\text{-C}_4\text{alkylene}$;

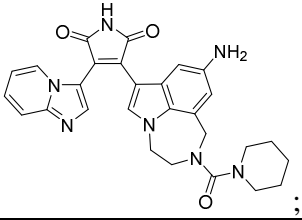
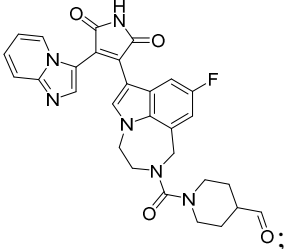
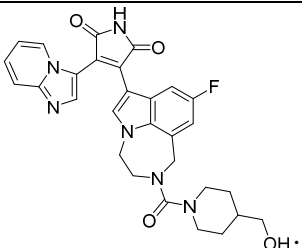
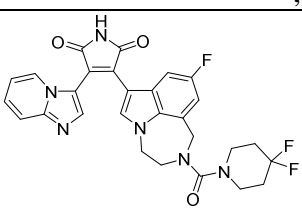
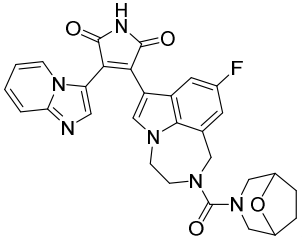
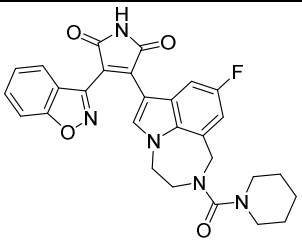
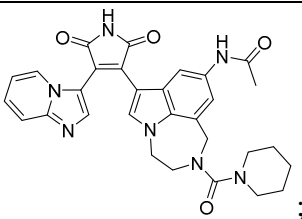
wherein R^{X1} is $\text{C}_3\text{-C}_8\text{cycloalkyl}$, heteroaryl, or heterocyclyl, wherein the heterocyclyl is optionally substituted with one to twelve substituents independently selected from the group consisting of deuterium, halo, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-CN}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_p\text{-OH}$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-OH}$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-O-C}_1\text{-C}_4\text{alkyl}$, $-\text{NHCOC}_1\text{-C}_4\text{alkyl}$, $\text{CONHC}_1\text{-C}_4\text{alkyl}$, COH , $-\text{CO}_2\text{H}$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-COO-C}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_p\text{-NH}_2$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-NH}_2$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-NH-C}_1\text{-C}_4\text{alkyl}$, $-\text{[C(R}^{X1a})_2\text{]}_p\text{-N-(C}_1\text{-C}_4\text{alkyl)}_2$; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, $-\text{CF}_3$, and $\text{C}_1\text{-C}_4\text{alkyl}$, or both R^{X1a} groups together form $\text{C}_3\text{-C}_6\text{cycloalkyl}$;

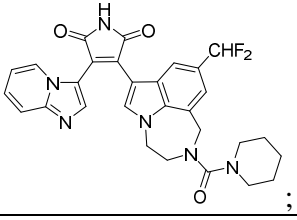
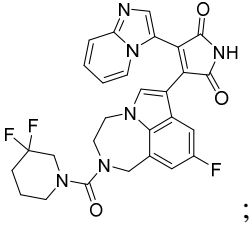
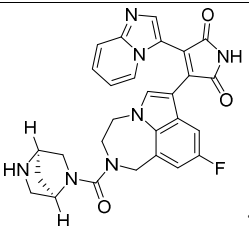
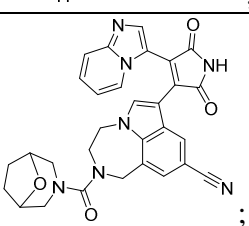
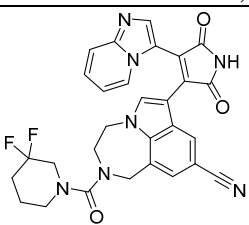
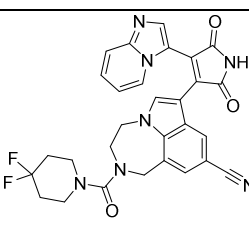
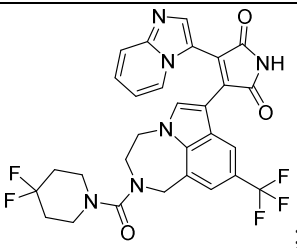
or R^{X1} is $\text{N(R}^{X2})_2$ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted alkyl, wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

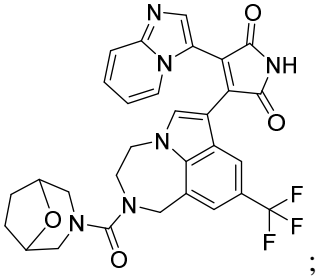
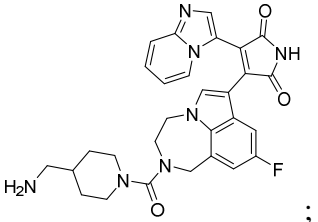
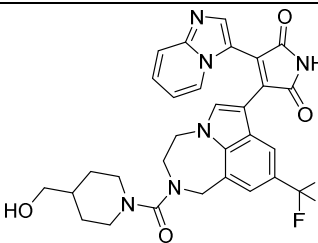
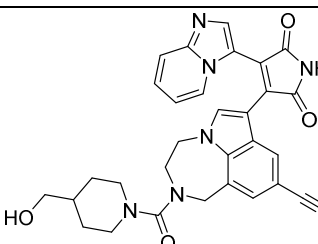
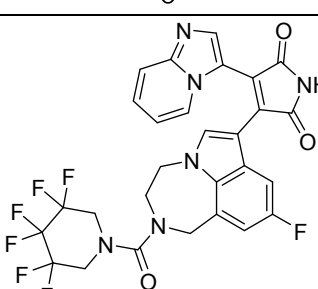
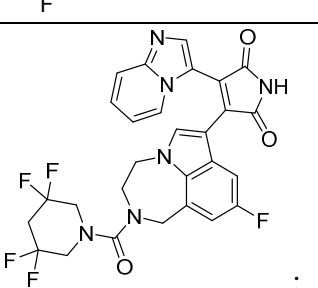
each R^Y is independently selected from the group consisting of hydrogen, deuterium, halo, and $\text{C}_1\text{-C}_4\text{alkyl}$, or both R^Y groups together form $\text{C}_3\text{-C}_6\text{cycloalkyl}$ or oxo; and m is 0, 1, or 2.

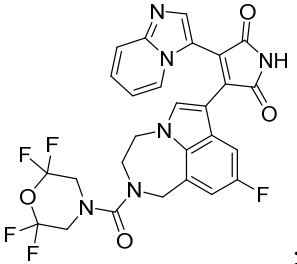
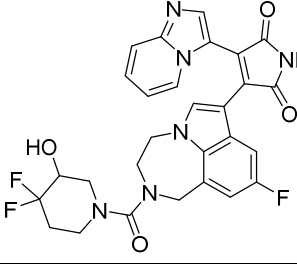
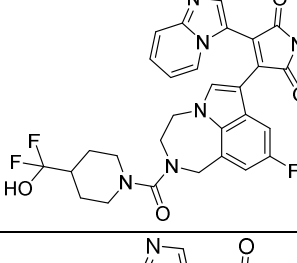
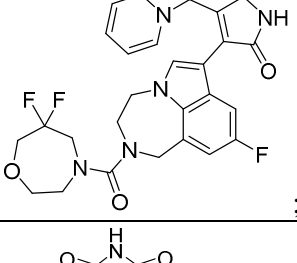
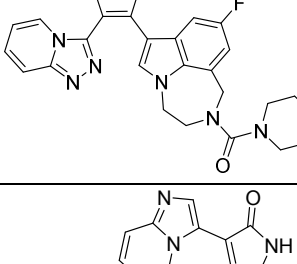
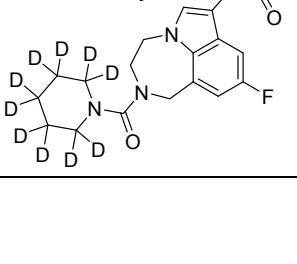
[0011b] In another aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from the group consisting of

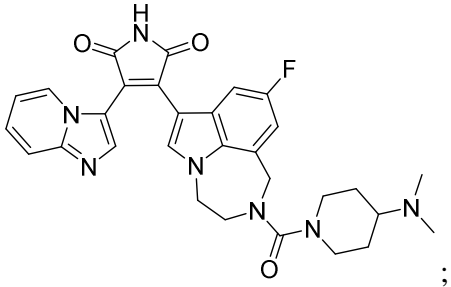
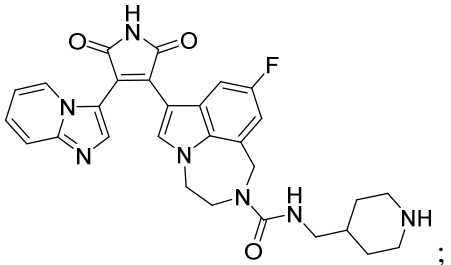
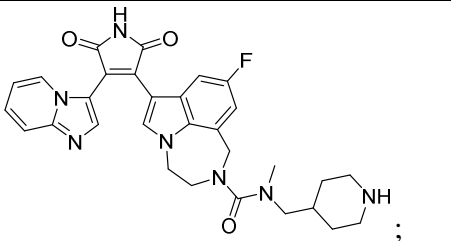
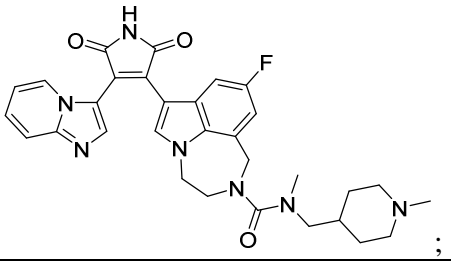
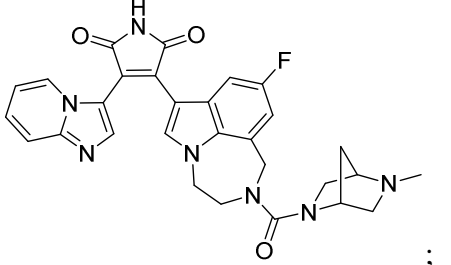
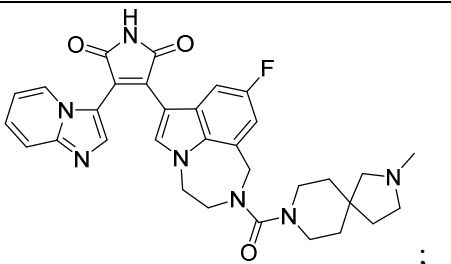
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Compound I-2	
Compound I-3	

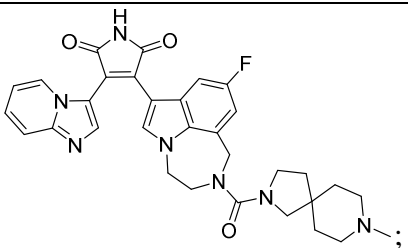
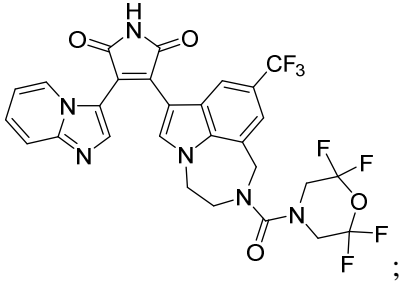
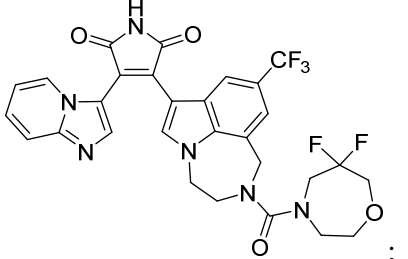
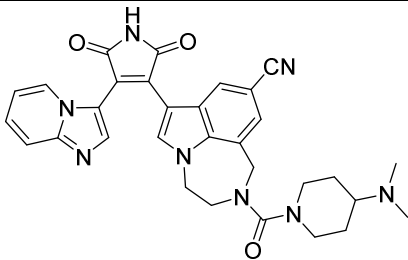
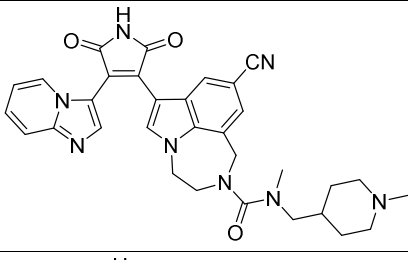
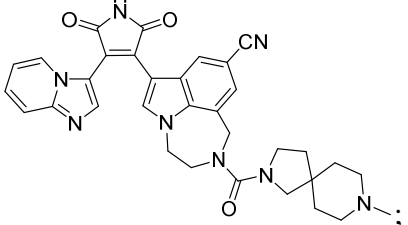
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Compound I-10	

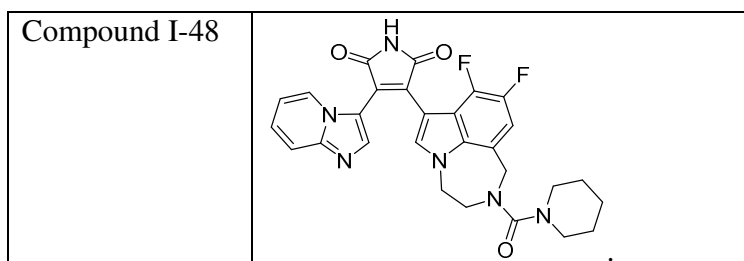
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Compound I-15	
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Compound I-17	

Compound I-18	
Compound I-19	
Compound I-20	
Compound I-21	
Compound I-22	
Compound I-23	

Compound I-24	 ;
Compound I-25	 ;
Compound I-26	 ;
Compound I-27	 ;
Compound I-28	 ;
Compound I-29	 ;

Compound I-36	
Compound I-37	
Compound I-38	
Compound I-39	
Compound I-40	
Compound I-41	

Compound I-42	
Compound I-43	
Compound I-44	
Compound I-45	
Compound I-46	
Compound I-47	 ; and



[0011c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, and a pharmaceutically acceptable carrier.

[0012] In one example the present disclosure provides a method for proliferation of stem cells comprising administering to a cell population an effective amount of a composition provided herein. In some examples, proliferation occurs in the absence of a notch activator or an HDAC inhibitor.

[0013] Among the various examples of the present disclosure, therefore, may be noted a method for activating the Wnt pathway in a cell population to increase the capacity of the population for self-renewal, *i.e.*, the capacity for repeated generation of daughter cells with equivalent proliferation and ‘cell fate specification’ potential, and differentiation, *i.e.*, the capacity for generation of daughter cells specified for differentiation. In one example, the cell population is a cochlear supporting cell population. Preferably, the Wnt pathway is activated upstream of the c-myc gene in members of the population and without any genetic modification of the population. Instead, the Wnt pathway is preferably activated by small molecules that transiently induce such activity. Additionally, the supporting cell population preferably includes supporting cells that are LGR5⁺ and endogenous to the Organ of Corti.

[0014] A further example of the present disclosure is a method for inducing the self-renewal of stem/progenitor supporting cells comprised by a cochlear cell population. That is, the stem/progenitor supporting cells are induced to proliferate (*i.e.*, divide and form daughter cells) while maintaining, in the daughter cells, the capacity to differentiate into hair cells. In contrast, if the stem/progenitor supporting cells were merely induced to proliferate (without maintaining multi-potency), the daughter cells would lack the capacity to divide into hair cells. Further, merely enforcing differentiation of a pre-existing stem/progenitor cell population has the

potential to exhaust the stem cell pool. Proliferation is preferably activated by small molecules that transiently induce such activity. Additionally, in certain examples the supporting cell population preferably includes supporting cells that are LGR5+ and endogenous to the Organ of Corti.

[0015] In a first example methods of using 1H-pyrrole-2,5-dione compounds for inducing the self-renewal of stem/progenitor supporting cells is provided. In some examples, 1H-pyrrole-2,5-dione compounds are compounds of Formula (I).

[0016] In certain examples, therefore, the present disclosure provides methods to induce self-renewal of a population of supporting cells by activating pathways and mechanisms that are known to be involved in inducing stem cell properties, such as those used to create “induced pluripotent stem cells”. Preferably, the pathways are activated with small molecules. For example, a compound when applied *in vitro* to a supporting cell population induces the population to proliferate to a high degree and in high purity in a Stem Cell Proliferation Assay, and also allows the population to differentiate into a high purity population of a tissue cell in a Stem Cell Differentiation Assay. In one such example, the compound induces and maintains stem cell properties by proliferating to produce stem cells that can divide for many generations and maintain the ability to have a high proportion of the resulting cells differentiate into tissue cells. Further, the proliferating stem cells express stem cell markers which may include one or more of Lgr5, Sox2, Opeml, Phex, lin28, Lgr6, cyclin D1, Msx1, Myb, Kit, Gdnf3, Zic3, Dppa3, Dppa4, Dppa5, Nanog, Esrrb, Rex1, Dnmt3a, Dnmt3b, Dnmt3l, Utf1, Tcf1, Oct4, Klf4, Pax6, Six2, Zic1, Zic2, Otx2, Bmi1, CDX2, STAT3, Smad1, Smad2, smad2/3, smad4, smad5, and smad7.

[0017] In certain examples, the disclosure provides a method for expanding a population of cochlear cells in a cochlear tissue comprising a parent population of cells. In this example, the method comprises contacting the cochlear tissue with a stem cell proliferator to form an expanded population of cells in the cochlear tissue, wherein

the stem cell proliferator is capable of (i) forming a proliferation assay final cell population from a proliferation assay initial cell population over a proliferation assay time period in a stem cell proliferation assay and (ii) forming a differentiation assay final cell population from a differentiation assay initial cell population over a differentiation assay time period in a stem cell differentiation assay wherein:

The assay described above does not include applying a notch activator or an HDAC inhibitor.

[0017a] In another aspect, the present disclosure refers to an in vitro method of expanding a population of cochlear cells in a cochlear tissue comprising a parent population, the method comprising contacting the cochlear tissue with a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein.

[0017b] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for expanding a population of cochlear cells in a cochlear tissue comprising a parent population, wherein the cochlear tissue is in a subject.

[0017c] In another aspect, the present disclosure refers to an in vitro or ex vivo method of facilitating the generation of tissue cells, the method comprising administering or causing to be administered to a stem cell population a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein.

[0017d] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for facilitating the generation of tissue cells, wherein the medicament is to be administered or caused to be administered to a stem cell population.

[0018] In certain examples, the disclosure provides a method for increasing the cell density of supporting cells in a population of cochlear cells. The method comprises activating pathways and mechanisms that induce stem cell properties in the supporting cells, proliferating the activated supporting cells (while maintaining the multi-potent character of the supporting cells in the newly formed daughter cells) and thereafter allowing (or even inducing) the expanded population to differentiate into hair cells to form an expanded cochlear cell population wherein the cell density of hair cells in the expanded cochlear cell population exceeds the cell density of hair cells in the original (non-expanded) cochlear cell population. In some

examples, such proliferation occurs in the absence of a notch activator or an HDAC inhibitor. In some examples, the supporting cell population is an *in vitro* supporting cell population. In other examples, the supporting cell population is an *in vivo* supporting cell population. Additionally, the proliferation stage is preferably controlled to substantially maintain the native organization of the cochlear structure. The proliferation is induced by the compound described herein that transiently induces such activity rather than by induction of c-myc and without any genetic modification of the population. In some examples, such proliferation occurs in the absence of a notch activator or an HDAC inhibitor. Additionally, in certain examples the supporting cell population preferably includes supporting cells that are LGR5⁺ and endogenous to the Organ of Corti.

[0019] In certain examples, the disclosure provides a method for increasing the cell density of Lgr5⁺ supporting cells in a population of cochlear cells. The method comprises activating pathways and mechanisms that induce or maintain stem cell properties in the Lgr5⁺ supporting cells, proliferating the activated Lgr5⁺ supporting cells (while maintaining such stem cell properties) and thereafter allowing (or even inducing) the expanded population to differentiate into hair cells to form an expanded cochlear cell population wherein the cell density of hair cells in the expanded cochlear cell population exceeds the cell density of hair cells in the original (non-expanded) cochlear cell population. In some examples for increasing the cell density of Lgr5⁺ supporting cells in a population of cochlear cells, such increasing of the cell density occurs in the absence of a notch activator or an HDAC inhibitor. In some examples, the Lgr5⁺ supporting cell population is an *in vitro* Lgr5⁺ stem cell population. In other

examples, the Lgr5⁺ supporting cell population is an *in vivo* supporting cell population.

Additionally, in certain examples the proliferation stage is preferably controlled to substantially maintain the native organization of the cochlear structure.

[0020] In certain examples, the disclosure provides a method for increasing the cell density of hair cells in an initial population of cochlear cells, the initial population (which may be an *in vivo* or an *in vitro* population) comprises hair cells, Lgr5⁻ supporting cells, and Lgr5⁺ supporting cells. In some examples for increasing the cell density of hair cells in an initial population of cochlear cells, such increasing of the cell density occurs in the absence of a notch activator or an HDAC inhibitor. The method comprises administering to the initial population a compound described herein.

[0021] In certain examples, the method produces stem cells in a Stem Cell Proliferation Assay that express stem cells markers Lgr5⁺. In certain examples, if a mixed population of Lgr5⁺ and non-Lgr5⁺ stems are placed in a Stem Cell Proliferation Assay, the method increases the fraction of cells in the population that are Lgr5⁺. In some examples, such production of stem cells in a Stem Cell Proliferation Assay occurs in the absence of a notch activator or an HDAC inhibitor.

[0022] Expanding supporting cell populations to a degree that destroys the native organization of the cochlear structure could inhibit cochlear function. Driving proliferation of existing supporting cells with a small molecule signal may allow for a more controlled regeneration of hair cells than using gene delivery, which is incapable of targeting a specific cell type and permanently alters a cell's genetic information. An approximately normal cochlear structure is desired with rows of hair cells that have supporting cells between them, and hair cells do not contact other hair cells. Further, it would be desirable to avoid using genetic modification to drive proliferation to create large cell aggregations in the cochlea that disrupt the organ's anatomy.

[0023] In certain examples, the disclosure provides a method for increasing the cell density of hair cells in an initial population of cochlear cells comprising hair cells and supporting cells. The method comprises selectively expanding the number of supporting cells in the initial population to form an intermediate cochlear cell population wherein the ratio of the number of supporting cells to hair cells in the intermediate cochlear cell population exceeds the ratio of the number of supporting cells to hair cells in the initial cochlear cell population. The method

further comprises generating hair cells in the intermediate cochlear cell population to form an expanded cochlear cell population wherein the ratio of the number of hair cells to supporting cells in the expanded cochlear cell population exceeds the ratio of the number of hair cells to supporting cells in the intermediate cochlear cell population. In some examples, the method does not comprise the use of a notch activator or an HDAC inhibitor.

[0023a] In another aspect, the present disclosure refers to an in vitro or ex vivo method of facilitating the generation of inner ear hair cells, the method comprising: administering a compound as described herein or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, to expand the stem cell population of cochlear tissue.

[0023b] In another aspect, the present disclosure refers to an in vitro or ex vivo method of regenerating hearing in mammals, the method comprising administering a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor.

[0023c] In another aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for facilitating the generation of inner ear hair cells, wherein the medicament is to be administered to a stem cell population of an in vivo subject.

[0023d] In another aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for regenerating hearing in mammals, wherein the medicament is to be administered to a stem cell population of an in vivo subject.

[0024] In certain examples, the disclosure provides a method for increasing the number of Lgr5⁺ supporting cells or increasing the Lgr5⁺ activity in an initial population of cochlear cells, wherein the initial population comprises supporting cells and hair cells. For example, in one such method an intermediate population is formed in which the number of Lgr5⁺ supporting cells is expanded relative to the initial population. Alternatively, in one such method an intermediate population is formed in which the Lgr5⁺ activity of the supporting cells relative to the initial population is increased. Alternatively, a method where the number of Lgr5⁺ cells is increased relative to the initial cell population by activating Lgr5⁺ expression in cell types that

normally lack or have very low levels of Lgr5⁺. In some examples, these alternative methods do not comprise the use of a notch activator or an HDAC inhibitor. By way of further example, an intermediate population is formed in which the number of Lgr5⁺ supporting cells is expanded and the Lgr5 activity is increased relative to the initial cochlear cell population. Thereafter, hair cells in the intermediate cochlear cell population may be generated to form an expanded cochlear cell population wherein the ratio of hair cells to supporting cells in the expanded cochlear cell population exceeds the ratio of the number of hair cells to supporting cells in the intermediate cochlear cell population.

[0025] In each of the afore mentioned examples of the present disclosure, stemness is induced by activating Wnt or inhibiting GSK3 activity. In some examples, inducing stemness does not comprise the use of a notch activator or an HDAC inhibitor.

[0026] In certain examples, the disclosure provides methods for preventing and treating auditory dysfunction. For example, in certain examples, the disclosure provides methods for preventing or treating auditory impairments in a subject comprising administering to said subject an effective amount of a compound provided herein.

[0027] In certain examples, the present disclosure also relates to ex-vivo uses of cells described herein. For example, approaches described herein can be used for high through screens and for discovery purposes. For example, certain examples of the present disclosure

are useful for identifying agents that proliferate hair cell progenitors and/or increase numbers of hair cells, and also agents that protect supporting cells and/or hair cells (*e.g.* to support their survival), and also for identifying agents that are toxic or not toxic to supporting cells or differentiated progeny including hair cells.

[0028] In certain examples, the disclosure provides for methods for inhibiting the loss or death of the cells of the auditory system in a subject comprising administering to said subject an effective amount of the compound described herein or derivative thereof or pharmaceutically acceptable salt thereof and an acceptable carrier or excipient, thereby inhibiting loss or death of the cells of the auditory system in the subject. In some examples, the method does not comprise the use of a notch activator or an HDAC inhibitor.

[0029] In certain examples, the disclosure provides methods for maintaining or promoting the growth of cells of the auditory system in a subject comprising administering to said subject the compound described herein or derivative thereof or pharmaceutically acceptable salt thereof in an effective amount so as to augment or initiate endogenous repair, thereby maintaining or promoting the growth of cells of the auditory system in the subject.

[0030] Also described herein is a method for expanding a population of cochlear cells in a cochlear tissue comprising a parent population of cells, the parent population including supporting cells and a number of Lgr5⁺ cells, the method comprising contacting the cochlear tissue with a stem cell proliferator to form an expanded population of cells in the cochlear tissue, wherein the stem cell proliferator is capable (i) in a stem cell proliferation assay of increasing the number of Lgr5⁺ cells in a stem cell proliferation assay cell population by a factor of at least 10 and (ii) in a stem cell differentiation assay of forming hair cells from a cell population comprising Lgr5⁺ cells. In some examples for expanding a population of cochlear cells, the method does not comprise the use of a notch activator or an HDAC inhibitor.

[0031] Also described herein is a method for expanding a population of cochlear cells in a cochlear tissue comprising a parent population of cells, the parent population including supporting cells, the method comprising contacting the cochlear tissue with a stem cell proliferator to form an expanded population of cells in the cochlear tissue. The stem cell proliferator can be capable of (i) forming a proliferation assay final cell population from a proliferation assay initial cell population over a proliferation assay time period in a stem cell proliferation assay and (ii) forming a differentiation assay final cell population from a

differentiation assay initial cell population over a differentiation assay time period in a stem cell differentiation assay wherein: (a) the proliferation assay initial cell population has (i) a proliferation assay initial number of total cells, (ii) a proliferation assay initial number of Lgr5⁺ cells, (iii) a proliferation assay initial number of hair cells, (iv) a proliferation assay initial Lgr5⁺ cell fraction that equals the ratio of the proliferation assay initial number of Lgr5⁺ cells to the proliferation assay initial number of total cells, and (v) a proliferation assay initial hair cell fraction that equals the ratio of the proliferation assay initial number of hair cells to the proliferation assay initial number of total cells; (b) the proliferation assay final cell population has (i) a proliferation assay final number of total cells, (ii) a proliferation assay final number of Lgr5⁺ cells, (iii) a proliferation assay final number of hair cells, (iv) a proliferation assay final Lgr5⁺ cell fraction that equals the ratio of the proliferation assay final number of Lgr5⁺ cells to the proliferation assay final number of total cells and (v) a proliferation assay final hair cell fraction that equals the ratio of the proliferation assay final number of hair cells to the proliferation assay final number of total cells; (c) the differentiation assay initial cell population has (i) a differentiation assay initial number of total cells, (ii) a differentiation assay initial number of Lgr5⁺ cells, (iii) a differentiation assay initial number of hair cells, (iv) a differentiation assay initial Lgr5⁺ cell fraction that equals the ratio of the differentiation assay initial number of Lgr5⁺ cells to the differentiation assay initial number of total cells, and (v) a differentiation assay initial hair cell fraction that equals the ratio of the differentiation assay initial number of hair cells to the differentiation assay initial number of total cells; (d) the differentiation assay final cell population has (i) a differentiation assay final number of total cells, (ii) a differentiation assay final number of Lgr5⁺ cells, (iii) a differentiation assay final number of hair cells, (iv) a differentiation assay final Lgr5⁺ cell fraction that equals the ratio of the differentiation assay final number of Lgr5⁺ cells to the differentiation assay final number of total cells, and (v) a differentiation assay final hair cell fraction that equals the ratio of the differentiation assay final number of hair cells to the differentiation assay final number of total cells; (e) the proliferation assay final number of Lgr5⁺ cells exceeds the proliferation assay initial number of Lgr5⁺ cells by a factor of at least 10; and (f) the differentiation assay final number of hair cells is a non-zero number. In some examples of the assay described above, the assay does not comprise the use of a notch activator or an HDAC inhibitor.

[0031a] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for generating inner ear hair cells, wherein the medicament proliferates LGR5+ cells in an initial population in vivo, resulting in an expanded population of LGR5+ cells, resulting in generation of inner ear hair cells.

[0031b] In another aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for facilitating generation of intestinal cells, to expand the stem cell population of intestinal epithelia.

[0031c] In another aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor in the manufacture of a medicament for expanding Lgr5+ cell population of intestinal epithelia.

[0031d] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament to regenerate Lgr5+ cell population intestinal cells in mammals.

[0031e] In another aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for proliferating Lgr5+ epithelial cells in vivo.

[0031f] In another aspect, the present disclosure refers to an in vitro method for expanding a population of vestibular cells in a vestibular tissue comprising contacting the vestibular tissue with (i) a compound as described herein or a pharmaceutically acceptable salt thereof, and (ii) a TGF- β Inhibitor to form an expanded population of cells in the vestibular tissue.

[0031g] In another aspect, the present disclosure refers to use of (i) a compound as described herein or a pharmaceutically acceptable salt thereof, and (ii) a TGF- β Inhibitor in the manufacture of a medicament for expanding a population of vestibular cells in a vestibular tissue, wherein the medicament forms an expanded population of cells in the vestibular tissue.

[0032] The proliferation assay final number of Lgr5⁺ cells can be greater than the proliferation assay initial number of Lgr5⁺ cells by a factor of at least 50, or by a factor of at least 100. The expanded population of cells in the cochlear tissue can include a greater number of hair cells than does the parent population. The proliferation assay final Lgr5⁺ cell fraction can be greater than the differentiation assay initial Lgr5⁺ cell fraction by at least a factor of 2. The differentiation assay final hair cell fraction can be greater than the proliferation assay initial hair cell fraction by at least a factor of 2. The proliferation assay final hair cell fraction can be at least 25% less than

the proliferation assay initial hair cell fraction. The proliferation assay final Lgr5⁺ cell fraction can be at least 10% greater than proliferation assay initial Lgr5⁺ cell fraction. One of more morphological characteristics of the cochlear tissue can be maintained. Native morphology can be maintained. The stem cell proliferator can be dispersed in a biocompatible matrix, which can be a biocompatible gel or foam. The cochlear tissue can be an in vivo cochlear tissue or an ex vivo cochlear tissue. The method can produce a population of Lgr5⁺ cells that are in s-phase. The cochlear tissue can be in a subject, and contacting the cochlear tissue with the compound can be achieved by administering the compound trans-tympanically to the subject. Contacting the cochlear tissue with the compound can result in improved auditory functioning of the subject.

[0033] Also described herein is a method of treating a subject who has, or is at risk of developing, hearing loss. The method can include trans-tympanically administering to a cochlear tissue of the subject compound provided herein.

[0033a] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells, wherein the medicament is to be administered to a stem cell population.

[0033b] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.

[0033c] In another aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, for use in treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells.

[0033d] In another aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, for use in treating a subject who has, or is at risk of developing, hearing loss.

[0033e] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells.

[0033f] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.

[0034] Also described herein is a method of generating Myo7a+ cochlear cells. The method can include contacting Lgr5+ cochlear cells with a compound provided herein, thereby generating an expanded population of Lgr5+ cells, thereby generating Myo7a+ cochlear cells.

[0035] Other objects and features will be in part apparent and in part pointed out hereinafter.

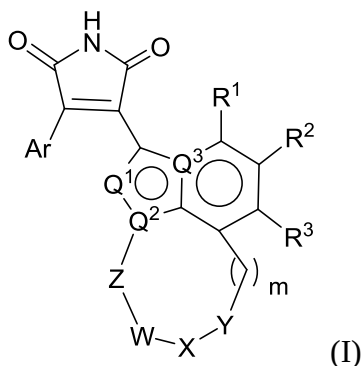
[0035a] In another aspect, the present disclosure refers to a system for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells, comprising: a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof; and a trans-tympanic administrative device.

Definitions

[0036] In this application, the use of “or” means “and/or” unless stated otherwise. As used in this application, the term “comprise” and variations of the term, such as “comprising” and “comprises,” are not intended to exclude other additives, components, integers or steps. As used in this application, the terms “about” and “approximately” are used as equivalents. Any numerals used in this application with or without about/approximately are meant to cover any normal fluctuations appreciated by one of ordinary skill in the relevant art. In certain

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt or tautomer thereof, wherein:

Q^1 is CH or N;

Q^2 is C or N;

Q^3 is C or N;

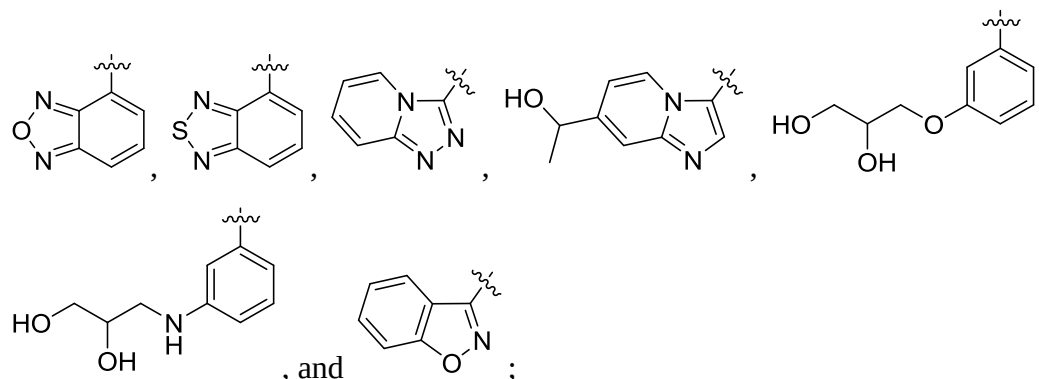
wherein at least one of Q^1 , Q^2 , and Q^3 is N;

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{1a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C_1 - C_4 alkyl;

R^2 is selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NH(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)₂, -NHC(O) R^{2a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C_1 - C_4 alkyl;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C_1 - C_4 alkyl;

Chemical structures of indazole, benzoxazole, and benzothiazole are shown, separated by commas. Each structure has a wavy line indicating a point of attachment.


$$\text{-Z-W-X-Y- is -C(R}^{\text{Z}}\text{)}_2\text{-C(R}^{\text{W}}\text{)}_2\text{-N(R}^{\text{X}}\text{)-C(R}^{\text{Y}}\text{)}_2\text{-, -C(R}^{\text{Z}}\text{)}_2\text{-C(R}^{\text{W}}\text{)}_2\text{-CH(R}^{\text{X}}\text{)-C(R}^{\text{Y}}\text{)}_2\text{-,}$$

each R^Z is independently selected from the group consisting of hydrogen, deuterium,

each R^W is independently selected from the group consisting of hydrogen, deuterium,

or R^Z and R^W together with the carbons to which they are attached form a C_3 -

R^x is selected from the group consisting of -COR^{x1}, -SO₂R^{x1}, heteroaryl, and -(C₁-
 lene)-(C₃-C₈cycloalkyl), and wherein the-(C₁-C₄alkylene)-(C₃-C₈cycloalkyl) is optionally
 uted with one to four halo on the C₁-C₄alkylene;

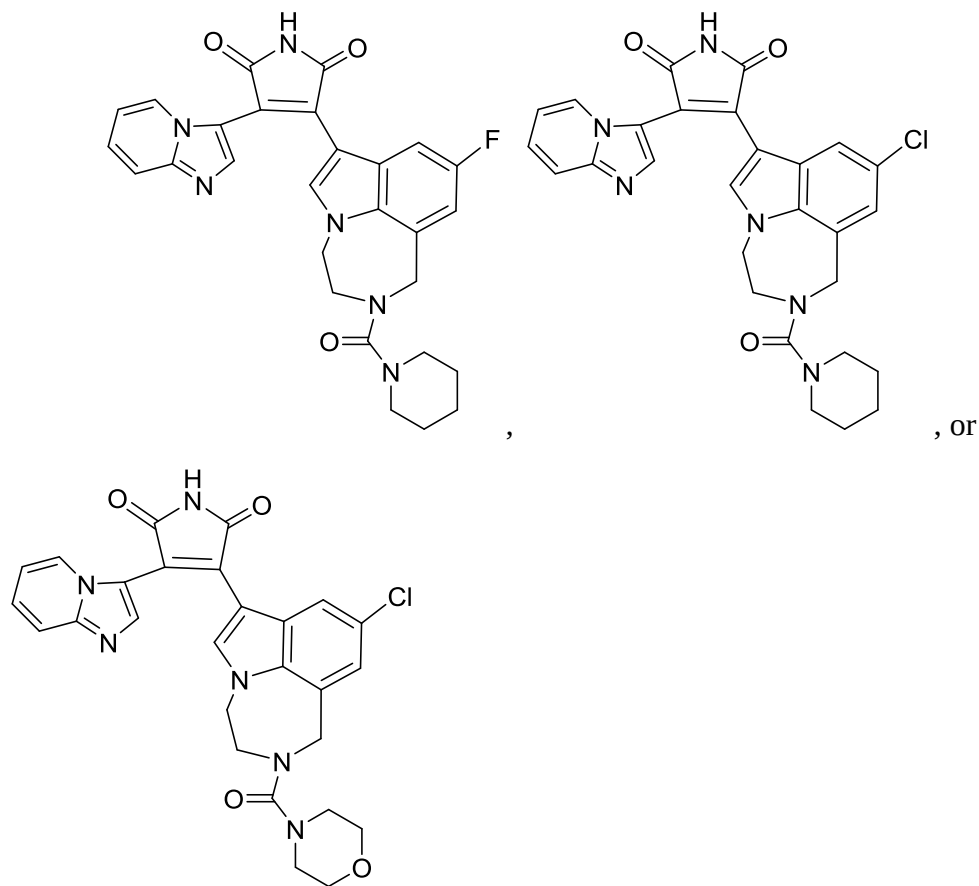
wherein R^{X1} is heterocyclyl, wherein the heterocyclyl is optionally substituted with one or two substituents independently selected from the group consisting of deuterium, halo, -C(=O)R^{X1a}, -C(R^{X1a})₂-CN, -CF₃, C₁-C₄alkyl, -(CH₂)_p-OH, -[C(R^{X1a})₂]p-OH, -[C(R^{X1a})₂]p-O-C₁-C₄alkyl, -C₁-C₄alkyl, -CONHC₁-C₄alkyl, -COH, -CO₂H, -[C(R^{X1a})₂]p-COO-C₁-C₄alkyl, -(CH₂)_p-C(R^{X1a})₂-NH₂, -[C(R^{X1a})₂]p-NH-C₁-C₄alkyl, -[C(R^{X1a})₂]p-N-(C₁-C₄alkyl)₂; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, -CF₃, and C₁-C₄alkyl, or both R^{X1a} groups together form C₃-C₆cycloalkyl;

or R^{X1} is $N(R^{X2})_2$ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

each R^Y is independently selected from the group consisting of hydrogen, deuterium,

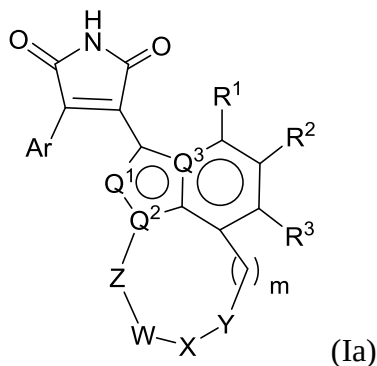
m is 0, 1, or 2;

provided that the compound is not



2. The compound of claim 1, wherein R^X is $-\text{COR}^{X1}$.
3. The compound of claim 2, wherein R^{X1} is piperidine, 2,8-diazaspiro[4,5]decane, 2,5-diazabicyclo[2,2,1]heptane, or 8-oxa-3-azabicyclo[3.2.1]octane, each of which is optionally substituted with one to twelve substituents independently selected from the group consisting of deuterium, halo, $\text{C}_1\text{-C}_4$ alkyl, $-\text{C}(\text{RX}^{1a})_2\text{-OH}$, $-(\text{CH}_2)_p\text{-NMe}_2$, $-(\text{CH}_2)_p\text{-NHMe}$, $-(\text{CH}_2)_p\text{-NH}_2$; wherein p is 0, 1, 2, or 3.
4. The compound of claim 3, wherein R^{X1} is piperidine, optionally substituted with one to six halo substituents.

5. The compound of claim 4, the piperidine is optionally substituted with $-[C(R^{X1a})_2]_p-$ OH, $-(CH_2)_p-NMe_2$.
6. The compound of claim 1, wherein R^X is heteroaryl.
7. The compound of claim 6, wherein the heteroaryl is monocyclic or bicyclic.
8. The compound of claim 6, wherein the heteroaryl contains one to three nitrogens.
9. The compound of claim 1, wherein R^X is $-(C_1-C_4\text{alkylene})-(C_3-C_8\text{cycloalkyl})$.
10. The compound of claim 9, wherein the $-(C_1-C_4\text{alkylene})-(C_3-C_8\text{cycloalkyl})$ is substituted with one or two halogens on the $C_1-C_4\text{alkylene}$.
11. The compound of claim 9, wherein the $C_3-C_8\text{cycloalkyl}$ is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
12. A compound of Formula (Ia):



or a pharmaceutically acceptable salt or tautomer thereof, wherein:

Q^1 is CH or N;

Q^2 is C or N;

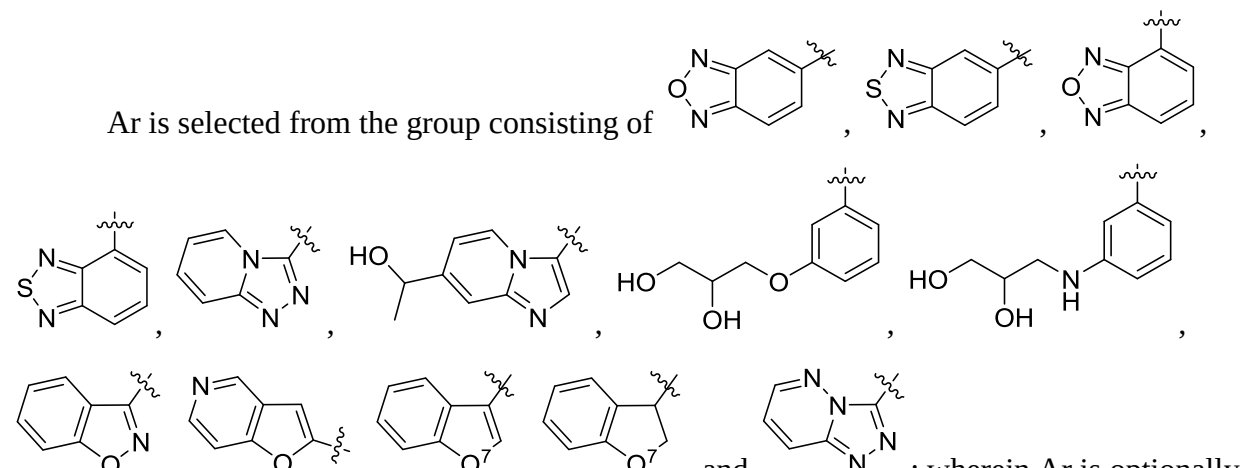
Q^3 is C or N;

wherein at least one of Q^1 , Q^2 , and Q^3 is N;

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C_1 - C_4 alkyl;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NH(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)₂, -NHC(O) R^{2a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{2a} is C_1 - C_4 alkyl;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_1 - C_4 alkynyl, -CN, -OH, -O- C_1 - C_4 alkyl, -NH₂, -NHC(O) R^{3a} , and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C_1 - C_4 alkyl;

Ar is selected from the group consisting of ; wherein Ar is optionally substituted with deuterium, halo, alkyl, alkoxy, and CN;

Q^7 is selected from S, O, CH₂, and NR^{Q7}; wherein R^{Q7} is hydrogen or optionally substituted C_1 - C_4 alkyl;

-Z-W-X-Y- is -C(R^Z)₂-C(R^W)₂-N(R^X)-C(R^Y)₂-, -C(R^Z)₂-C(R^W)₂-CH(R^X)-C(R^Y)₂-, or -C(R^W)₂-CH(R^X)-C(R^Y)₂-;

each R^Z is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^Z groups together form C_3 - C_6 cycloalkyl or oxo;

each R^W is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^W groups together form C_3 - C_6 cycloalkyl or oxo;

or R^Z and R^W together with the carbons to which they are attached form a C_3 - C_6 cycloalkyl;

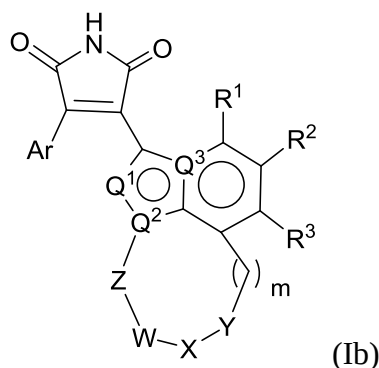
R^X is selected from the group consisting of hydrogen, R^{X1} , $-\text{COR}^{X1}$, $-\text{SO}_2\text{R}^{X1}$, $-(\text{C}_1\text{-C}_4\text{alkylene})\text{-R}^{X1}$, and wherein the $-(\text{C}_1\text{-C}_4\text{alkylene})\text{-R}^{X1}$ is optionally substituted with one to four halo on the $\text{C}_1\text{-C}_4\text{alkylene}$;

wherein R^{X1} is $\text{C}_3\text{-C}_8$ cycloalkyl, heteroaryl, or heterocyclyl, wherein the heterocyclyl is optionally substituted with one to twelve substituents independently selected from the group consisting of deuterium, halo, $-\text{[C(R}^{X1a})_2]_p\text{-CN}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_p\text{-OH}$, $-\text{[C(R}^{X1a})_2]_p\text{-OH}$, $-\text{[C(R}^{X1a})_2]_p\text{-O-C}_1\text{-C}_4\text{alkyl}$, $-\text{NHCOC}_1\text{-C}_4\text{alkyl}$, $\text{CONHC}_1\text{-C}_4\text{alkyl}$, COH , $-\text{CO}_2\text{H}$, $-\text{[C(R}^{X1a})_2]_p\text{-COO-C}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_p\text{-NH}_2$, $-\text{[C(R}^{X1a})_2]_p\text{-NH}_2$, $-\text{[C(R}^{X1a})_2]_p\text{-NH-C}_1\text{-C}_4\text{alkyl}$, $-\text{[C(R}^{X1a})_2]_p\text{-N-(C}_1\text{-C}_4\text{alkyl)}_2$; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, $-\text{CF}_3$, and $\text{C}_1\text{-C}_4\text{alkyl}$, or both R^{X1a} groups together form $\text{C}_3\text{-C}_6$ cycloalkyl;

or R^{X1} is $\text{N(R}^{X2})_2$ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted alkyl, wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

each R^Y is independently selected from the group consisting of hydrogen, deuterium, halo, and $\text{C}_1\text{-C}_4\text{alkyl}$, or both R^Y groups together form $\text{C}_3\text{-C}_6$ cycloalkyl or oxo; and
 m is 0, 1, or 2.

13. A compound of Formula (Ib):



or a pharmaceutically acceptable salt or tautomer thereof, wherein:

Q^1 is CH or N;

Q^2 is C or N;

Q^3 is C or N;

R¹ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{3a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{1a} is C₁-C₄alkyl;

R³ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{3a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and wherein R^{3a} is C₁-C₄alkyl;

each Q⁶ is independently selected from CR^{Q6} and N; wherein CR^{Q6} is hydrogen, halo, -CN, lower alkyl, or substituted alkyl;

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-Z-W-X-Y- is $-C(R^Z)_2-C(R^W)_2-N(R^X)-C(R^Y)_2-$, $-C(R^Z)_2-C(R^W)_2-CH(R^X)-C(R^Y)_2-$, or $-C(R^W)_2-CH(R^X)-C(R^Y)_2-$;

each R^Z is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^Z groups together form C_3 - C_6 cycloalkyl or oxo;

each R^W is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^W groups together form C_3 - C_6 cycloalkyl or oxo;

or R^Z and R^W together with the carbons to which they are attached form a C_3 - C_6 cycloalkyl;

R^X is selected from the group consisting of hydrogen, R^{X1} , $-COR^{X1}$, $-SO_2R^{X1}$, $-(C_1-C_4\text{alkylene})-R^{X1}$, and wherein the $-(C_1-C_4\text{alkylene})-R^{X1}$ is optionally substituted with one to four halo on the C_1 - C_4 alkylene;

wherein R^{X1} is C_3 - C_8 cycloalkyl, heteroaryl, or heterocyclyl, wherein the heterocyclyl is optionally substituted with one to twelve substituents independently selected from the group consisting of deuterium, halo, $-[C(R^{X1a})_2]_p-CN$, $-CF_3$, C_1 - C_4 alkyl, $-(CH_2)_p-OH$, $-[C(R^{X1a})_2]_p-OH$, $-[C(R^{X1a})_2]_p-O-C_1-C_4$ alkyl, $-NHCOC_1-C_4$ alkyl, $CONHC_1-C_4$ alkyl, COH , $-CO_2H$, $-[C(R^{X1a})_2]_p-COO-C_1-C_4$ alkyl, $-(CH_2)_p-NH_2$, $-[C(R^{X1a})_2]_p-NH_2$, $-[C(R^{X1a})_2]_p-NH-C_1-C_4$ alkyl, $-[C(R^{X1a})_2]_p-N-(C_1-C_4\text{alkyl})_2$; wherein p is 0, 1, 2, or 3; wherein each R^{X1a} is independently selected from the group consisting of hydrogen, deuterium, halo, $-CF_3$, and C_1 - C_4 alkyl, or both R^{X1a} groups together form C_3 - C_6 cycloalkyl;

or R^{X1} is $N(R^{X2})_2$ wherein R^{X2} is independently selected from hydrogen, alkyl, substituted alkyl, wherein the alkyl substitution can be halo, heterocycles and substituted heterocycles;

each R^Y is independently selected from the group consisting of hydrogen, deuterium, halo, and C_1 - C_4 alkyl, or both R^Y groups together form C_3 - C_6 cycloalkyl or oxo; and

m is 0, 1, or 2.

14. The compound of any one of claims 1-12, wherein Q^1 is CH; Q^2 is N; and Q^3 is C.

15. The compound of any one of claims 1-13, wherein Q^1 is N; Q^2 is C; and Q^3 is N.

16. The compound of any one of claims 1-13, wherein Q^1 is CH; Q^2 is C; and Q^3 is N.

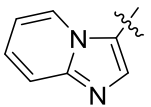
17. The compound of any one of claims 1-13, wherein Q^1 is N; Q^2 is N; and Q^3 is C.

18. The compound of any one of claims 1-17, wherein R^1 is hydrogen or halo.

19. The compound of any one of claims 1-18, wherein R^2 is halo.

20. The compound of any one of claims 1-18, wherein R^2 is selected from the group consisting of halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{C}\equiv\text{CH}$, $-\text{NH}_2$, and $-\text{NHC}(\text{O})\text{CH}_3$.

21. The compound of any one of claims 1-20, wherein R^3 is hydrogen or halo.

22. The compound of any one of claims 1 and 13-21, wherein Ar is .

23. The compound of any one of claims 1-22, wherein $-\text{Z}-\text{W}-\text{X}-\text{Y}-$ is $-\text{C}(\text{R}^Z)_2-\text{C}(\text{R}^W)_2-\text{N}(\text{R}^X)-\text{C}(\text{R}^Y)_2-$.

24. The compound of any one of claims 1-22, wherein $-\text{Z}-\text{W}-\text{X}-\text{Y}-$ is $-\text{C}(\text{R}^Z)_2-\text{C}(\text{R}^W)_2-\text{CH}(\text{R}^X)-\text{C}(\text{R}^Y)_2-$.

25. The compound of any one of claims 23-24, wherein each R^Z is independently selected from the group consisting of hydrogen and halo.

26. The compound of any one of claims 23-24, wherein both R^Z groups together form C_3 - C_6 cycloalkyl.

27. The compound of any one of claims 1-24, wherein R^Z and R^W together with the carbons to which they are attached form a C_3 - C_6 cycloalkyl.

28. The compound of any one of claims 1-22, wherein $-\text{Z}-\text{W}-\text{X}-\text{Y}-$ is $-\text{C}(\text{R}^W)_2-\text{CH}(\text{R}^X)-\text{C}(\text{R}^Y)_2-$.

29. The compound of any one of claims 1-28, wherein each R^W is independently selected from the group consisting of hydrogen and halo.

30. The compound of any one of claims 1-28, wherein both R^W groups together form C₃-C₆cycloalkyl.

31. The compound of any one of claims 1-30, wherein each R^Y is independently selected from the group consisting of hydrogen and halo.

32. The compound of any one of claims 1-30, wherein both R^Y groups together form C₃-C₆cycloalkyl.

33. The compound of any one of claims 12-32, wherein R^X is R^{X1} , wherein R^{X1} is heteroaryl.

34. The compound of any one of claims 12-32, wherein R^X is $-COR^{X1}$.

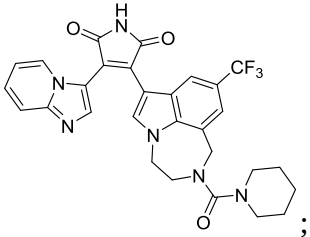
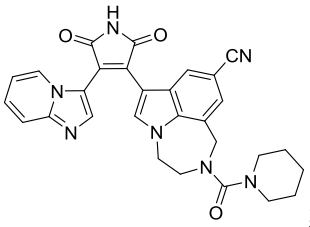
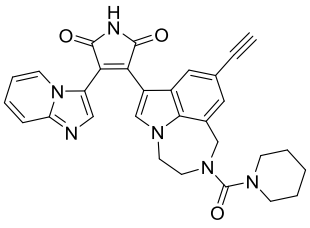
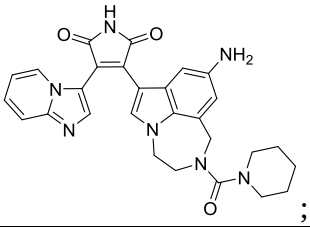
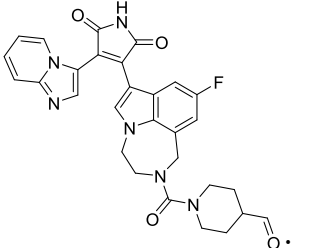
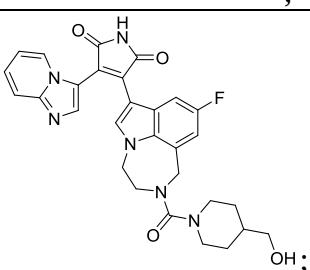
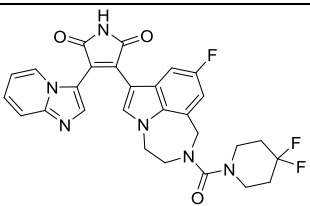
35. The compound of any one of claims 12-32, wherein R^X is $-SO_2R^{X1}$.

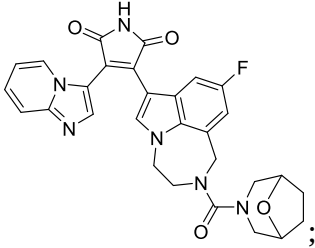
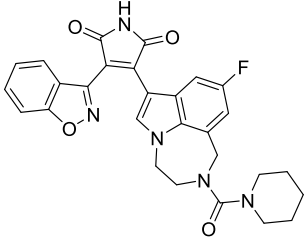
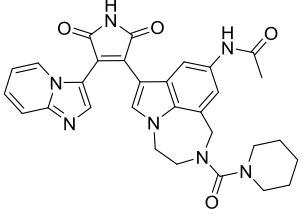
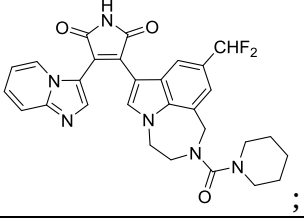
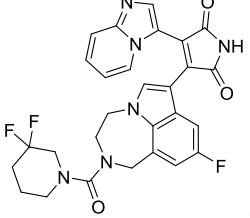
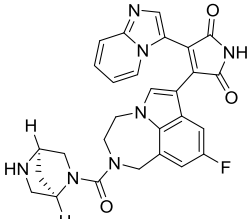
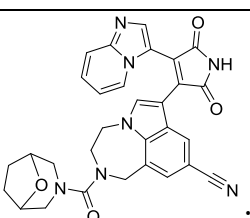
36. The compound of any one of claims 12-32, wherein R^X is $-(C_1-C_4\text{alkylene})-R^{X1}$.

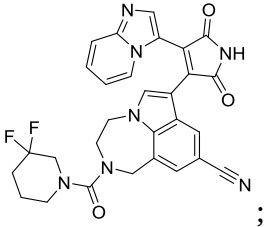
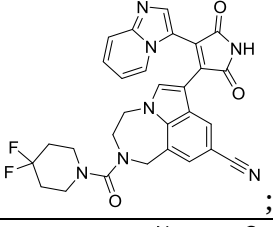
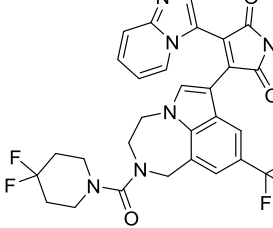
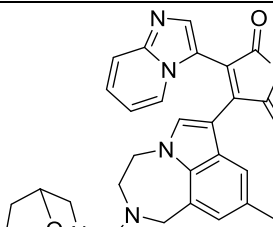
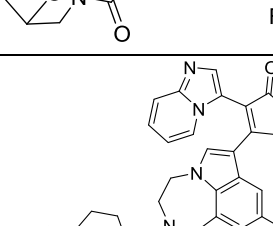
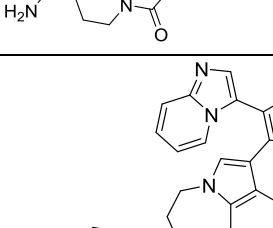
37. The compound of any one of claims 34-36, wherein R^{X1} is C₃-C₈cycloalkyl.

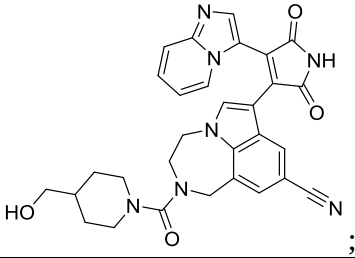
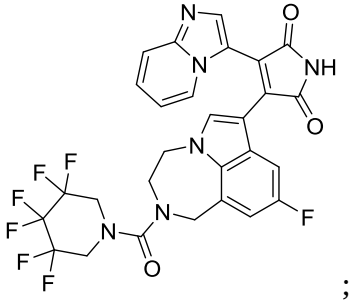
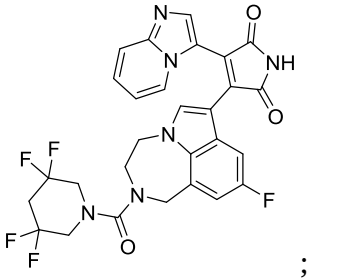
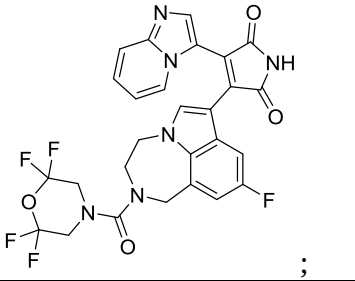
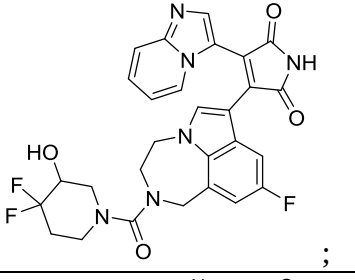
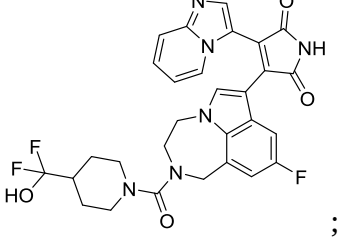
38. The compound of any one of claims 34-36, wherein R^{X1} is heterocyclyl, wherein the heterocyclyl is optionally substituted with one to twelve substituents that is halo.

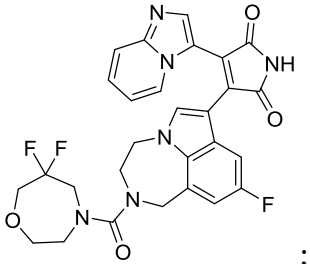
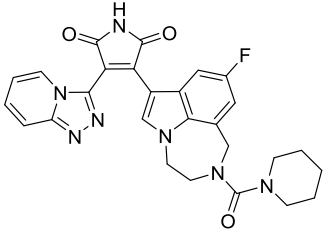
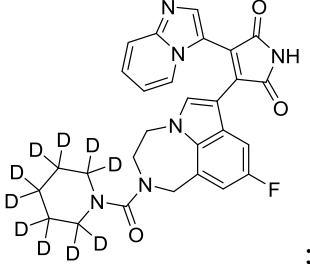
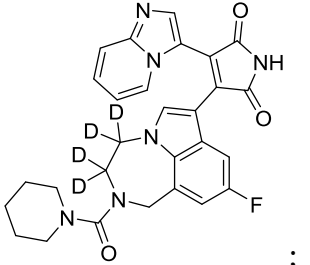
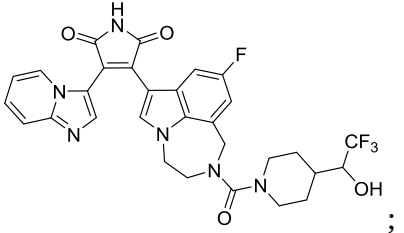
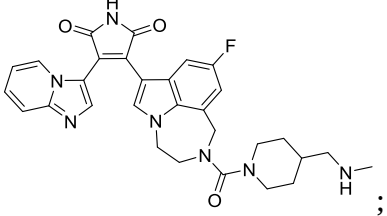
39. A compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from the group consisting of

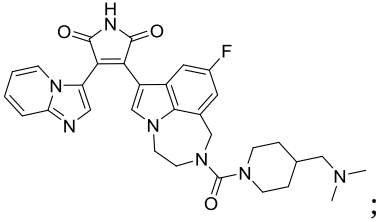
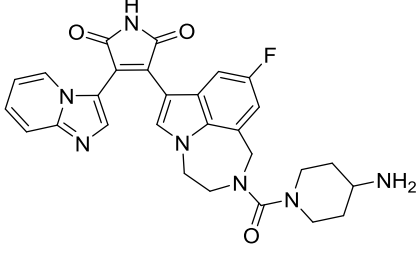
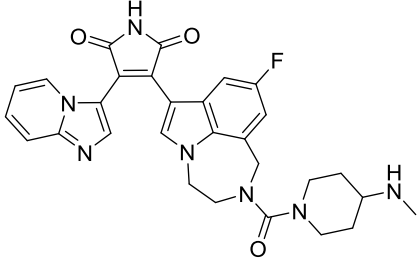
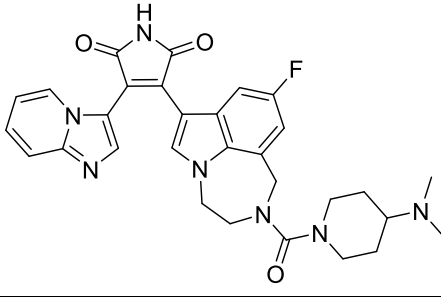
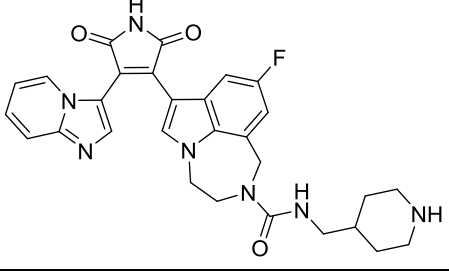
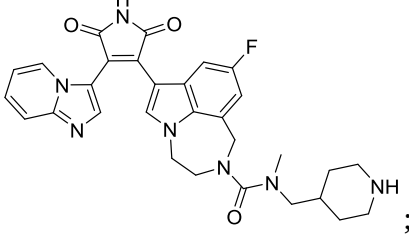
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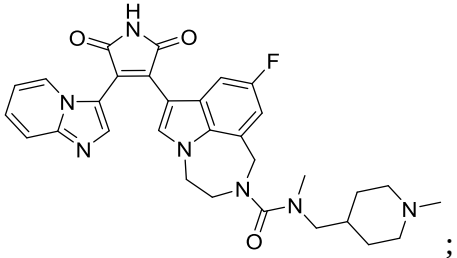
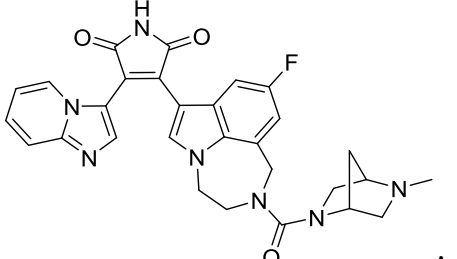
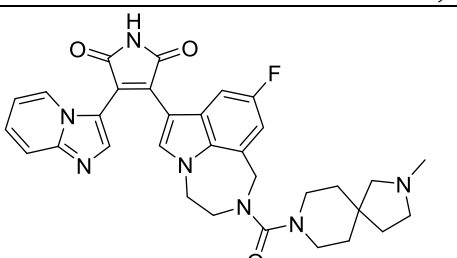
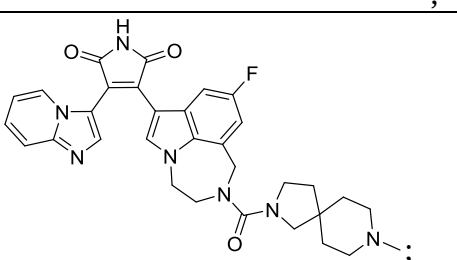
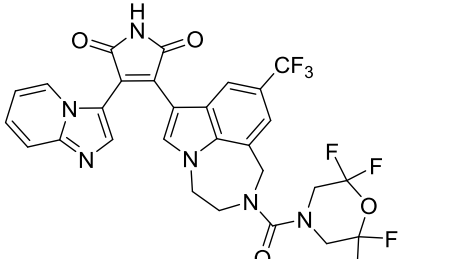
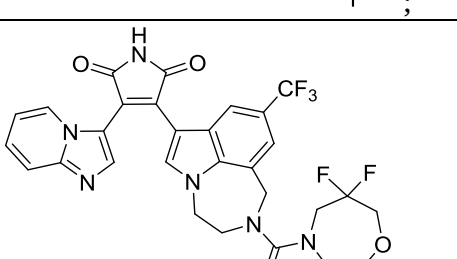
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Compound I-13	
Compound I-14	

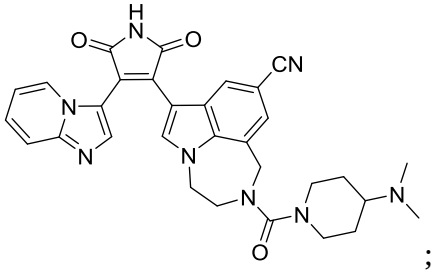
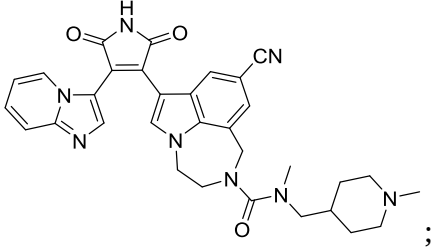
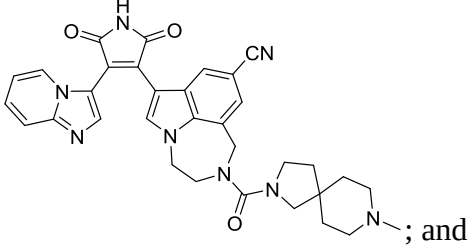
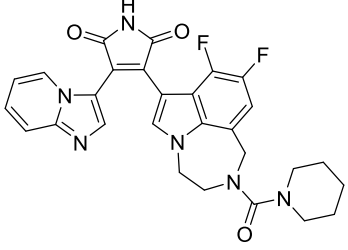
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Compound I-42	
Compound I-43	
Compound I-44	

Compound I-45	
Compound I-46	
Compound I-47	
Compound I-48	

40. A pharmaceutical composition comprising a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, and a pharmaceutically acceptable carrier.
41. The pharmaceutical composition of claim 40, further comprising HDAC inhibitor.
42. The pharmaceutical composition of claim 40, further comprising TGF beta inhibitor.
43. The pharmaceutical composition of claim 40, further comprising BMP inhibitor.
44. The pharmaceutical composition of any one of claims 40-43, further comprising poloxamer.

45. An in vitro method of expanding a population of cochlear cells in a cochlear tissue comprising a parent population, the method comprising contacting the cochlear tissue with a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44.
46. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44 in the manufacture of a medicament for expanding a population of cochlear cells in a cochlear tissue comprising a parent population, wherein the cochlear tissue is in a subject.
47. The use of claim 46, wherein the composition is to be administered trans-tympanically to the subject.
48. The use of claim 47, wherein the medicament results in improved auditory functioning of the subject.
49. An in vitro or ex vivo method of facilitating the generation of tissue cells, the method comprising administering or causing to be administered to a stem cell population a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44.
50. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44 in the manufacture of a medicament for facilitating the generation of tissue cells, wherein the medicament is to be administered or caused to be administered to a stem cell population.
51. The method of claim 49 or the use of claim 50, wherein the tissue cells are cochlear cells.
52. The method or use of claim 51, wherein the tissue cells are inner ear hair cells.

53. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44 in the manufacture of a medicament for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells, wherein the medicament is to be administered to a stem cell population.

54. The use of claim 53, wherein the tissue cells are cochlear cells.

55. The use of claim 53, wherein the tissue cells are inner ear hair cells.

56. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof or a pharmaceutical composition of any one of claims 40-44 in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.

57. The use of claim 56, wherein the compound is to be administered trans-tympanically to a cochlear tissue of the subject.

58. An in vitro or ex vivo method of facilitating the generation of inner ear hair cells, the method comprising: administering a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, to expand the stem cell population of cochlear tissue.

59. An in vitro or ex vivo method of regenerating hearing in mammals, the method comprising administering a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor.

60. Use of a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for facilitating the generation of inner ear hair cells, wherein the medicament is to be administered to a stem cell population of an in vivo subject.

61. Use of a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for regenerating hearing in mammals, wherein the medicament is to be administered to a stem cell population of an in vivo subject.

62. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for generating inner ear hair cells, wherein the medicament proliferates LGR5+ cells in an initial population in vivo, resulting in an expanded population of LGR5+ cells, resulting in generation of inner ear hair cells.

63. Use of a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for facilitating generation of intestinal cells, to expand the stem cell population of intestinal epithelia.

64. The use of claim 63, wherein the intestinal epithelia is regenerated.

65. The use of claim 63, wherein the medicament is for promoting repair of damaged mucosa related to chemotherapy-induced gastrointestinal mucositis, Graph Versus Host Disease, gastric ulcer, Crohns, or ulcerative colitis.

66. Use of a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor in the manufacture of a medicament for expanding Lgr5+ cell population of intestinal epithelia.

67. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament to regenerate Lgr5+ cell population intestinal cells in mammals.

68. The use of claim 67, wherein the medicament is for promoting the repair of damaged mucosa related to chemotherapy-induced gastrointestinal mucositis, Graph Versus Host Disease, gastric ulcer, Crohns, or ulcerative colitis.

69. Use of a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for proliferating Lgr5⁺ epithelial cells in vivo.

70. An in vitro method for expanding a population of vestibular cells in a vestibular tissue comprising contacting the vestibular tissue with (i) a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, and (ii) a TGF- β Inhibitor to form an expanded population of cells in the vestibular tissue.

71. Use of (i) a compound of any one of claims 1-39 or a pharmaceutically acceptable salt thereof, and (ii) a TGF- β Inhibitor in the manufacture of a medicament for expanding a population of vestibular cells in a vestibular tissue, wherein the medicament forms an expanded population of cells in the vestibular tissue.

72. A system for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells, comprising:

a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof; and a trans-tympanic administrative device.

73. A compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, for use in treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells.

74. A compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, for use in treating a subject who has, or is at risk of developing, hearing loss.

75. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells.

76. Use of a compound of any one of claims 1-39, or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.