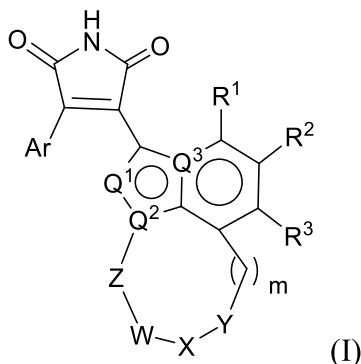


m is 0, 1, or 2.

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



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;

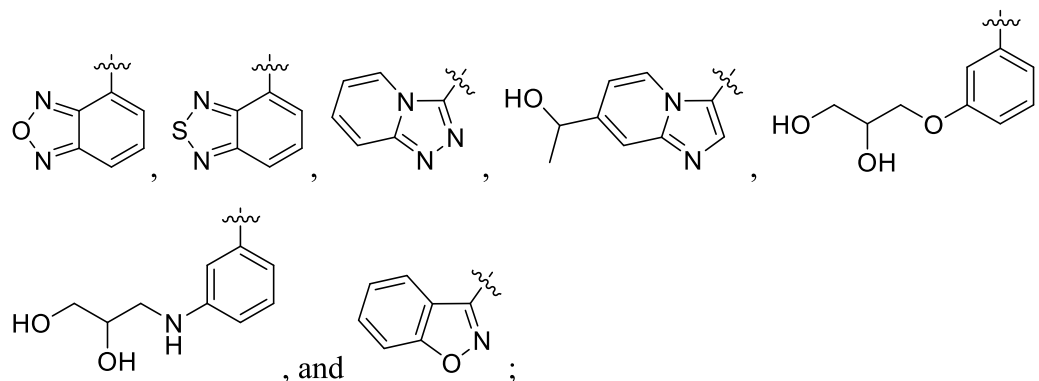
R¹ is selected from the group consisting of hydrogen, halo, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkynyl, -CN, -OH, -O-C₁-C₄alkyl, -NH₂, -NHC(O)R^{1a}, and -S(O)₂NH₂; wherein the alkyl is optionally substituted with one to 3 substituents independently selected from the group consisting of halo and -OH; and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

R² is selected from the group consisting of fluoro, 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 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;







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

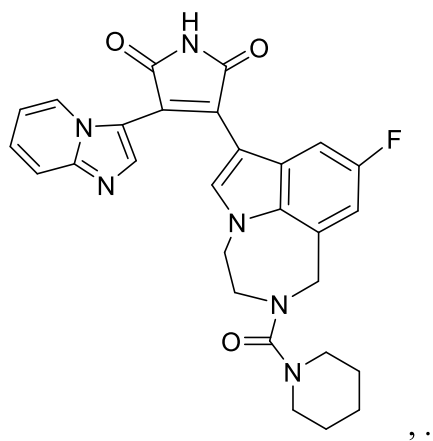
or R^Z and R^W together with the carbons to which they are attached form a C₃-alkyl;

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(=O)N(R^{X1a})₂, -C(=O)OR^{X1a}, -C(=O)NR^{X1a}R^{X1a}, -C(=O)N(R^{X1a})C(=O)R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})₂, -C(=O)N(R^{X1a})C(=O)OR^{X1a}, -C(=O)N(R^{X1a})C(=O)NR^{X1a}R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})₂, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)OR^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)NR^{X1a}R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})₂, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)OR^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)NR^{X1a}R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)R^{X1a}, -C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})C(=O)N(R^{X1a})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;

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

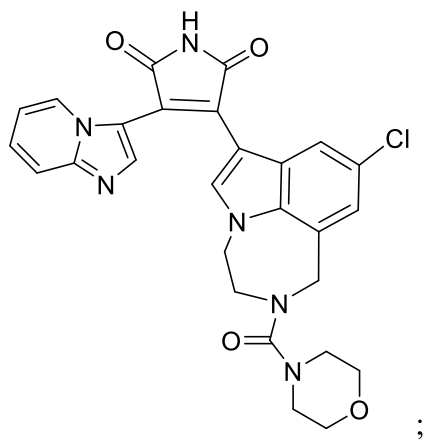
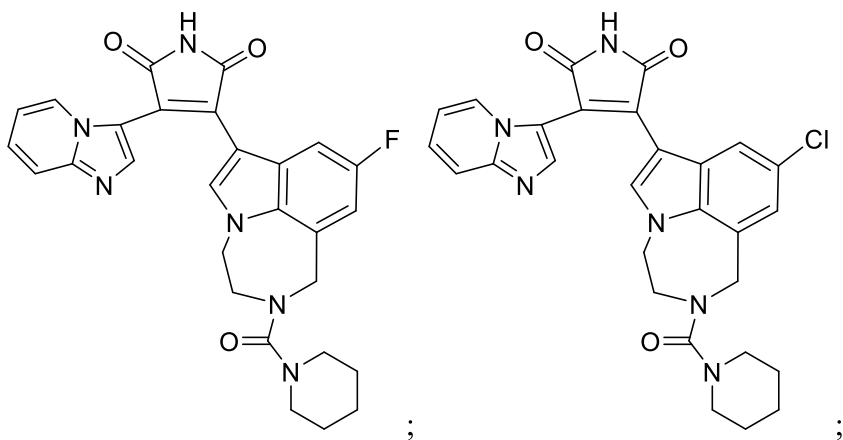
m is 0, 1, or 2;

provided that the compound is not

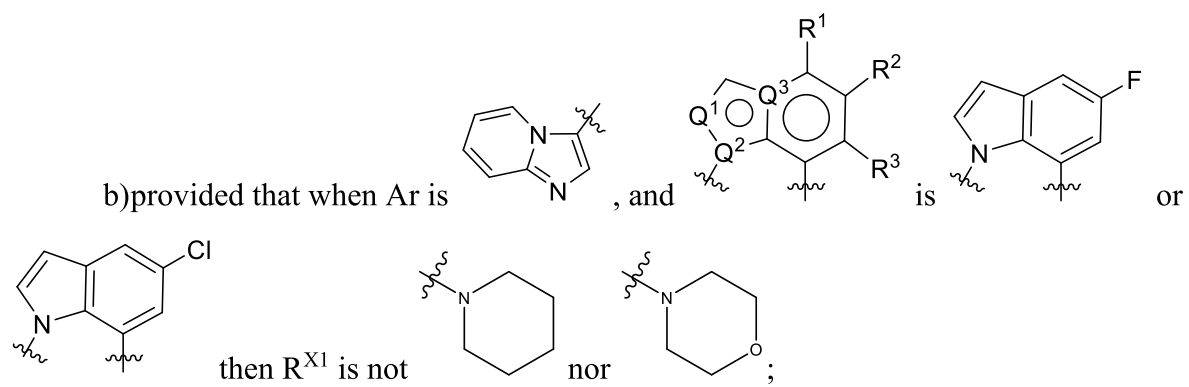


[0009] In some examples, the compounds of Formula (I) have one or more of the following features:

a) provided that the compound is not



or



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

[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 pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or tautomer thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[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

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

[0017a] In another aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt 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.

[0017b] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for facilitating the generation of tissue cells.

[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

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 use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.

[0023b] 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 a population of stem cells in the cochlear tissue.

[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

[0031a] 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 a population of Lgr5⁺ 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 expanding a population of stem cells in the intestinal epithelium.

[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 a population of Lgr5⁺ cells in the intestinal epithelium.

[0031d] 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.

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

[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.

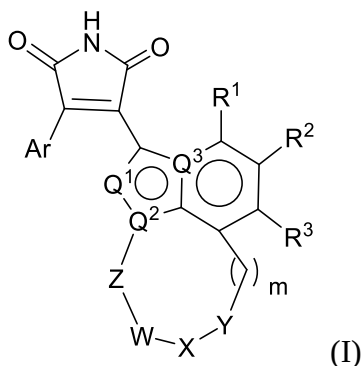
[0035a] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, a disease associated with absence or lack of certain tissue cells, wherein: the compound as described herein, or the pharmaceutically acceptable salt or tautomer thereof; is to be used in a system with 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:

Q¹ is CH or N;

Q² is C or N;

Q³ is C or N;

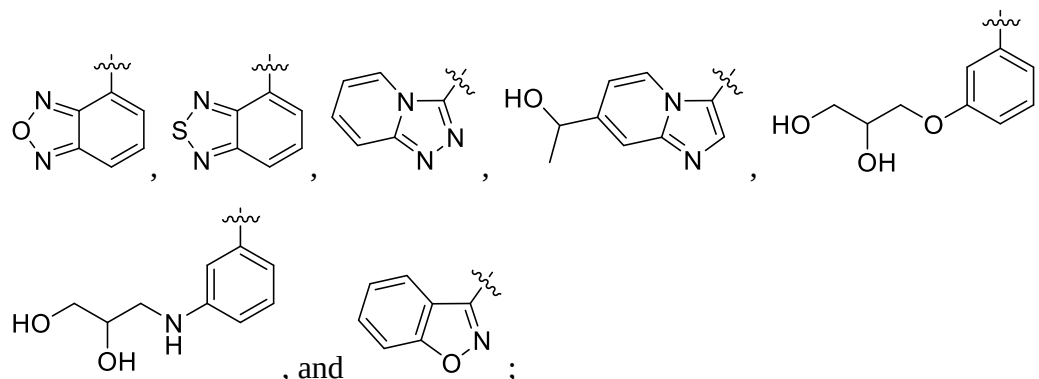
wherein at least one of Q¹, Q², and Q³ is N;

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 fluoro, 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 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.



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

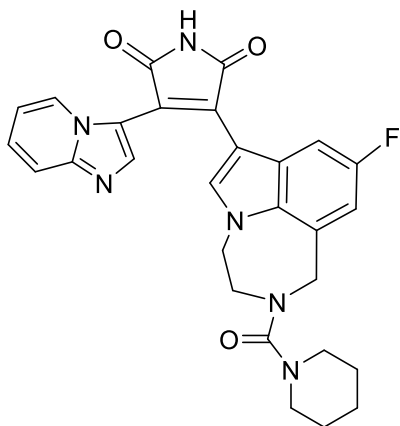
or R^Z and R^W together with the carbons to which they are attached form a C₃-alkyl;

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;

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

m is 0, 1, or 2;

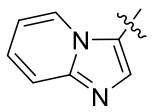
provided that the compound is not



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, $-\text{C}(\text{R}^{X1a})_2\text{p-OH}$, $-(\text{CH}_2)_\text{p}\text{-NMe}_2$, $-(\text{CH}_2)_\text{p}\text{-NHMe}$, $-(\text{CH}_2)_\text{p}\text{-NH}_2$; 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 $-\text{C}(\text{R}^{X1a})_2\text{p-OH}$, $-(\text{CH}_2)_\text{p}\text{-NMe}_2$.
6. The compound of claim 1, wherein the heteroaryl is monocyclic or bicyclic.
7. The compound of claim 1, wherein the heteroaryl contains one to three nitrogens.
8. The compound of claim 1, wherein Q^1 is CH; Q^2 is N; and Q^3 is C.
9. The compound of claim 1, wherein R^1 is hydrogen or halo.

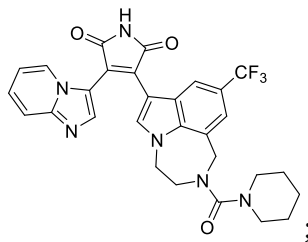
10. The compound of claim 1, wherein R^2 is fluoro.
11. The compound of claim 1, wherein R^2 is selected from the group consisting of fluoro, $-CF_3$, $-CN$, $-C\equiv CH$, $-NH_2$, and $-NHC(O)CH_3$.
12. The compound of claim 1, wherein R^3 is hydrogen or halo.

13. The compound of claim 1, wherein Ar is

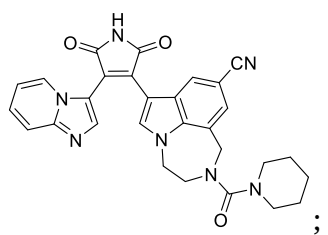


14. The compound of claim 1, wherein $-Z-W-X-Y-$ is $-C(R^Z)_2-C(R^W)_2-N(R^X)-C(R^Y)_2-$.
15. The compound of claim 14, wherein each R^Z is independently selected from the group consisting of hydrogen and halo.
16. The compound of claim 1, wherein each R^W is independently selected from the group consisting of hydrogen and halo.
17. The compound of claim 1, wherein each R^Y is independently selected from the group consisting of hydrogen and halo.
18. The compound of claim 1, selected from the group consisting of

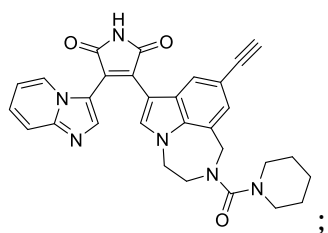
Compound I-1



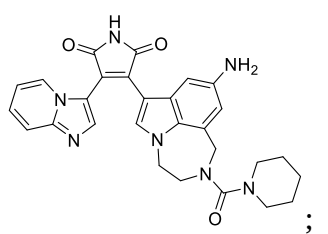
Compound I-2



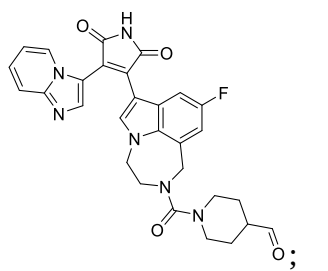
Compound I-3



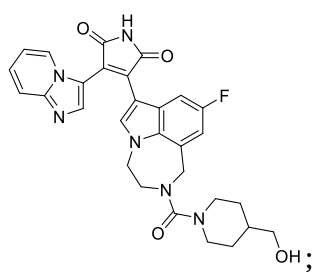
Compound I-4



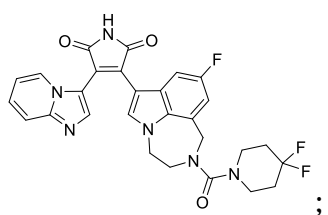
Compound I-5



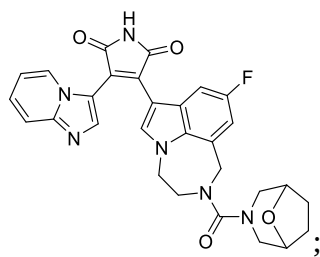
Compound I-6



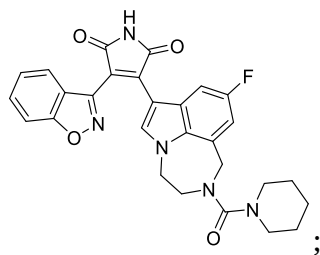
Compound I-7



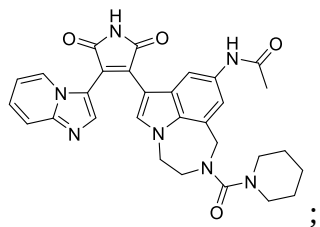
Compound I-8



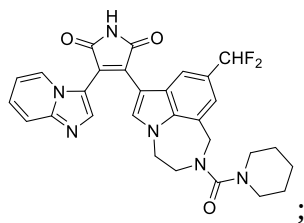
Compound I-9



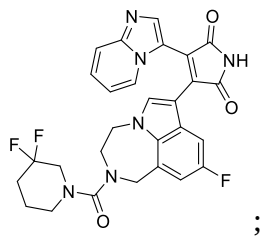
Compound I-10



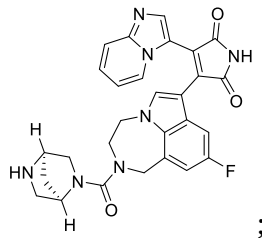
Compound I-11



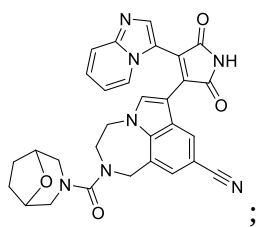
Compound I-12



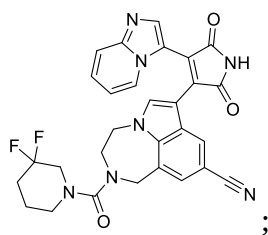
Compound I-13



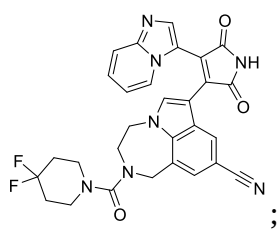
Compound I-14



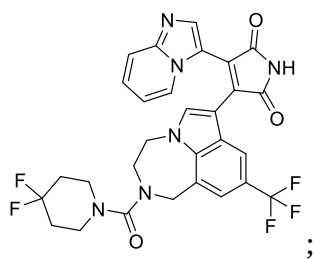
Compound I-15



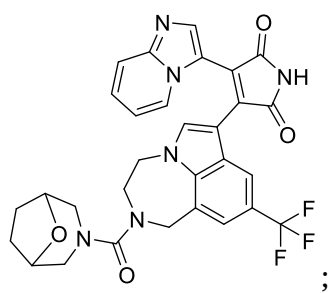
Compound I-16



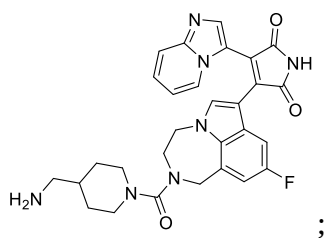
Compound I-17



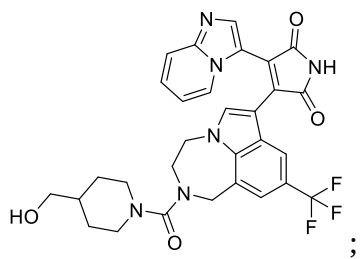
Compound I-18



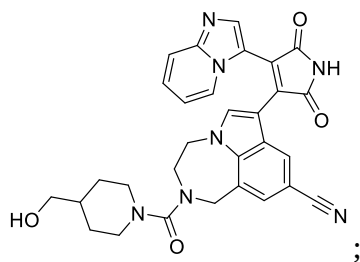
Compound I-19



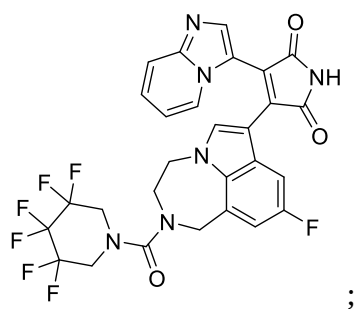
Compound I-20



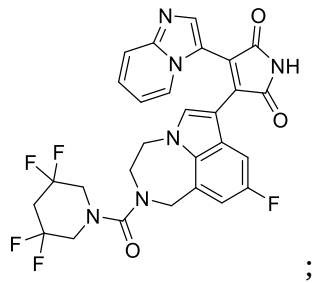
Compound I-21



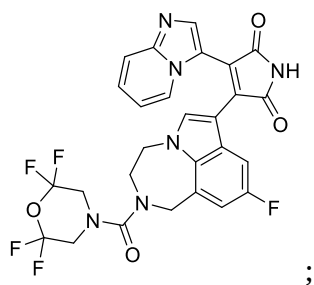
Compound I-22



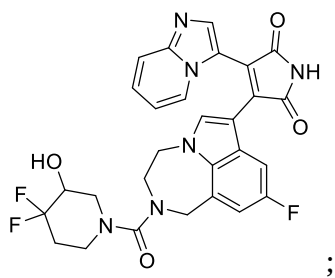
Compound I-23



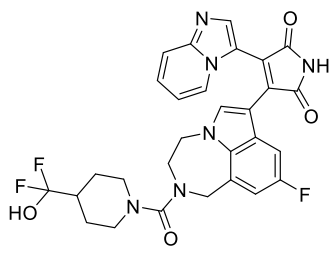
Compound I-24



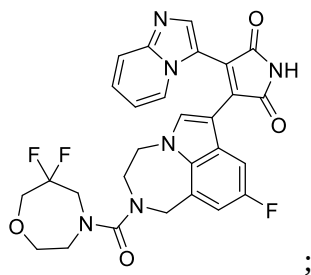
Compound I-25



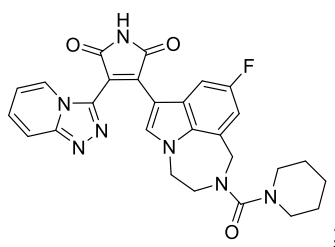
Compound I-26



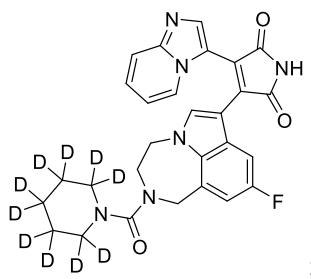
Compound I-27



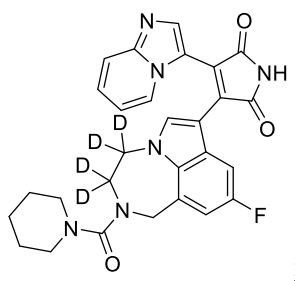
Compound I-28



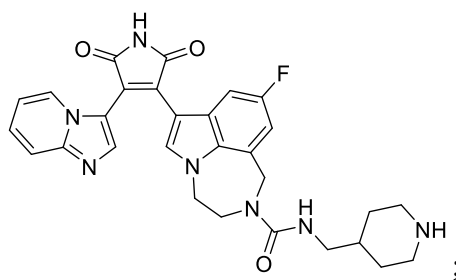
Compound I-29



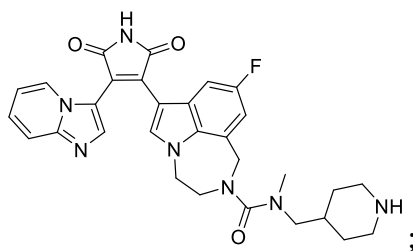
Compound I-30



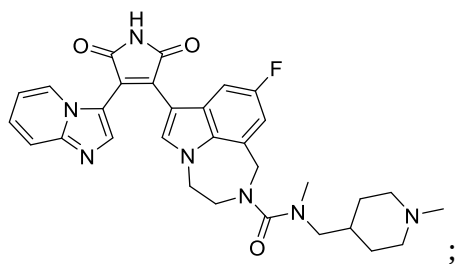
Compound I-37



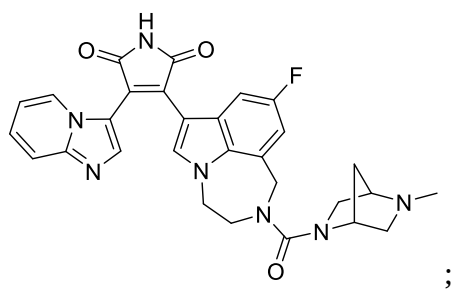
Compound I-38



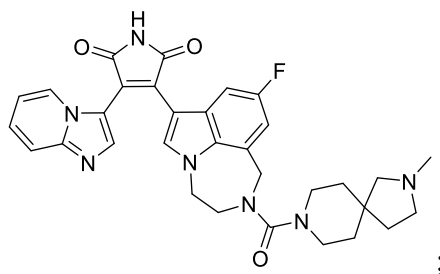
Compound I-39



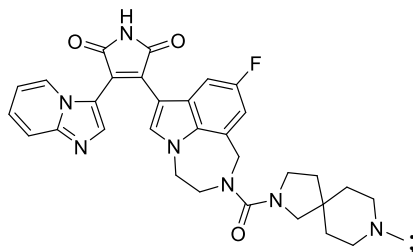
Compound I-40



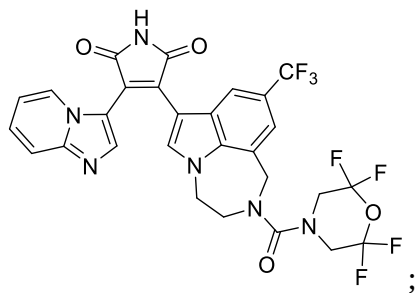
Compound I-41



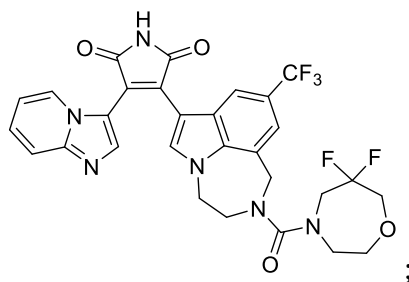
Compound I-42



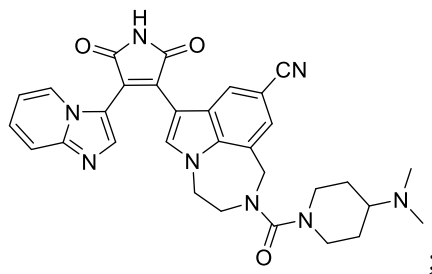
Compound I-43



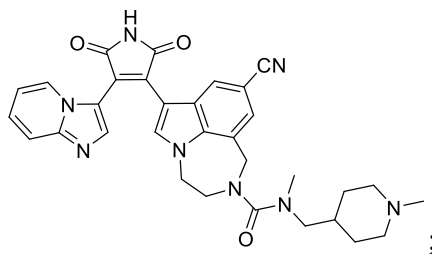
Compound I-44



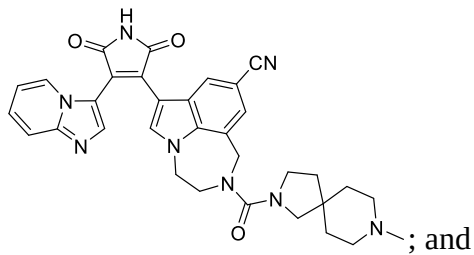
Compound I-45



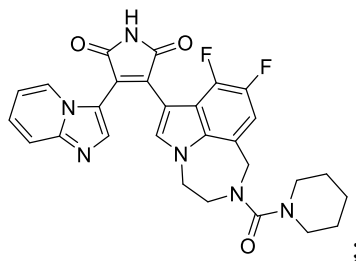
Compound I-46



Compound I-47

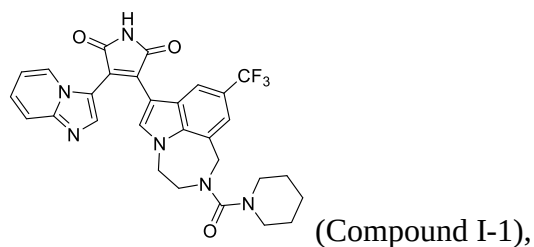


Compound I-48



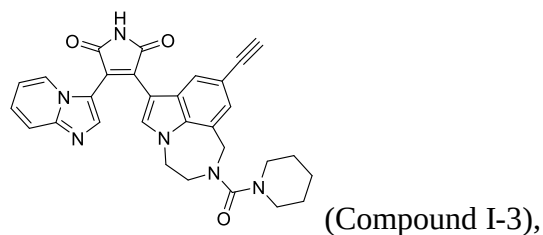
and pharmaceutically acceptable salts and tautomers thereof.

19. The compound of claim 18, wherein the compound is Compound I-1:



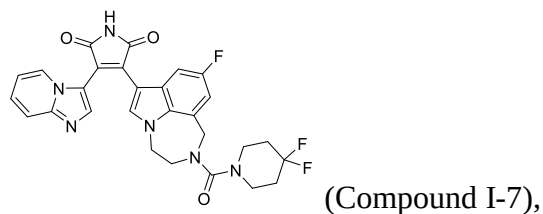
or a pharmaceutically acceptable salt or tautomer thereof.

20. The compound of claim 18, wherein the compound is Compound I-3:



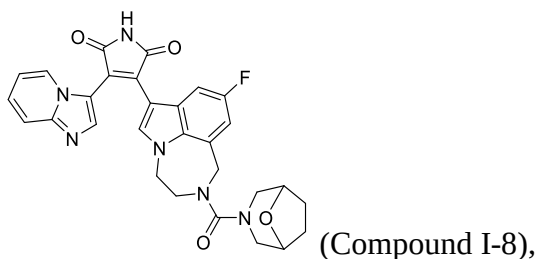
or a pharmaceutically acceptable salt or tautomer thereof.

21. The compound of claim 18, wherein the compound is Compound I-7:



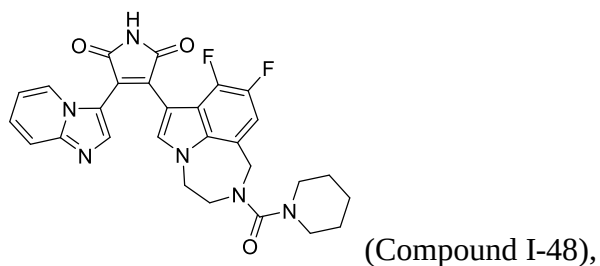
or a pharmaceutically acceptable salt or tautomer thereof.

22. The compound of claim 18, wherein the compound is Compound I-8:



or a pharmaceutically acceptable salt or tautomer thereof.

23. The compound of claim 18, wherein the compound is Compound I-48:



or a pharmaceutically acceptable salt or tautomer thereof.

24. A pharmaceutical composition comprising a compound of any one of claims 1-23, or a pharmaceutically acceptable salt or tautomer thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

25. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 24, in the manufacture of a medicament for expanding a population of cochlear cells in a cochlear tissue.

26. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 24, in the manufacture of a medicament for facilitating the generation of tissue cells.

27. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 24 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.
28. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 24, in the manufacture of a medicament for treating a subject who has, or is at risk of developing, hearing loss.
29. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for expanding a population of stem cells in the cochlear tissue.
30. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for expanding a population of Lgr5+ cells.
31. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor, in the manufacture of a medicament for expanding a population of stem cells in the intestinal epithelium.
32. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, alone or in combination with an HDAC inhibitor in the manufacture of a medicament for expanding a population of Lgr5+ cells in the intestinal epithelium
33. Use of a compound of any one of claims 1–23 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for proliferating Lgr5+ epithelial cells in vivo.
34. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for expanding a population of vestibular cells in a vestibular tissue, comprising (i) the compound, or the pharmaceutically acceptable salt thereof to

be contacted with the vestibular tissue, and (ii) a TGF- β Inhibitor, wherein the contacting results in an expanded population of vestibular cells in the vestibular tissue.

35. Use of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt 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, wherein:

the compound, or the pharmaceutically acceptable salt or tautomer thereof is to be used in a system with a trans-tympanic administrative device.