

In some examples, the chemical entities described herein are agonists (e.g. full agonists) of the APJ receptor. In other examples, the chemical entities described herein are partial agonists of the APJ receptor.

5 In other examples, the chemical entities described herein modulate (e.g., agonize) the APJ receptor in a pathway-specific manner. Accordingly, this disclosure also features chemical entities that exhibit activity as ligand-biased modulators (e.g., ligand-biased agonists). APJ receptor activity can modulate (e.g., alter or bias) competing levels of downstream G-protein signaling (activation) and β -arrestin recruitment. APJ receptor
10 signaling through β -arrestin has been shown to mediate stretch-induced myocardial hypertrophy. See, e.g., Scimia, M.C., *et al.*, *Nature* **2012**, 488, 394–398. In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) β -arrestin signaling. In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) recruitment of β -arrestin.

15 In certain examples, the chemical entities described herein activate or increase the levels of downstream G-protein signaling.

In certain examples, the chemical entities described herein inhibit or decrease the levels of β -arrestin recruitment.

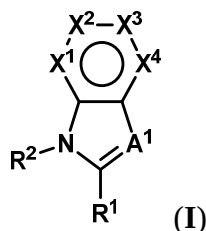
In certain examples, the chemical entities described herein activate or increase the
20 levels of β -arrestin recruitment.

In certain examples, the chemical entities described herein selectively modulate (e.g., increase) one of the pathways over the other. For example, the chemical entities described herein can activate or increase the levels of downstream G-protein signaling, and inhibit or decrease the levels of β -arrestin recruitment.

25 In other examples, the chemical entities described herein can activate or increase the levels of downstream G-protein signaling, and activate or increase the levels of β -arrestin recruitment. For example, the chemical entities described herein can fully agonize both β -arrestin and G protein signaling pathways.

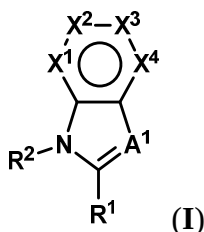
Generally, a receptor exists in an active (Ra) and an inactive (Ri) conformation. Certain compounds that affect the receptor can alter the ratio of Ra to Ri (Ra/Ri). For example, a full agonist increases the ratio of Ra/Ri and can cause a "maximal", saturating effect. A partial agonist, when bound to the receptor, gives a response that is lower than that elicited by a full agonist (e.g., an endogenous agonist). Thus, the Ra/Ri for a partial agonist is less than for a full agonist. However, the potency of a partial agonist may be greater or less than that of the full agonist.

In one example, the featured chemical entities include compounds of Formula I, or a pharmaceutically acceptable salt thereof:



in which **R¹**, **R²**, **A¹**, **X¹**, **X²**, **X³**, and **X⁴** can be as defined anywhere herein.

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



or a pharmaceutically acceptable salt thereof;

wherein:

A¹ is CH or N;

each of **X¹**, **X²**, **X³**, and **X⁴** is independently selected from the group consisting of N and **CR³**;

R¹ is:

(i) **-(Y¹)_n-Y²**, wherein:

- **n** is 0 or 1;
- **Y¹** is C₁₋₆ alkylene, which is optionally substituted with from 1-6 **R^a**; and
- **Y²** is:

- (a) C₃₋₁₀ cycloalkyl, which is optionally substituted with from 1-4 **R^b**;
- (b) C₆₋₁₀ aryl, which is optionally substituted with from 1-4 **R^c**;
- (c) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**, or
- (d) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^b**,

OR

(ii) -**Z¹**-**Z²**-**Z³**, wherein:

- **Z¹** is C₁₋₃ alkylene, which is optionally substituted with from 1-4 **R^a**;
- **Z²** is -N(H)-, -N(**R^d**)-, -O-, or -S-; and
- **Z³** is C₂₋₇ alkyl, which is optionally substituted with from 1-4 **R^a**;

OR

(iii) C₃₋₁₀ alkyl, optionally substituted with from 1-6 independently selected **R^a**;

OR

(iv) -**Z⁴**-**Z⁵**-**Z⁶**-**Y²** wherein:

- **Z⁴** is C₁₋₃ alkylene, which is optionally substituted with from 1-4 **R^a**;
- **Z⁵** is -N(H)-, -N(**R^d**)-, -O-, or -S-;
- **Z⁶** is C₁₋₄ alkylene, which is optionally substituted with from 1-4 **R^a**; and
- **Y²** is as defined above;

R² is:

(i) C₆₋₁₀ aryl, which is optionally further substituted with from 1-4 **R^c**;

(ii) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**),

O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**;

(iii) C₃₋₁₀ cycloalkyl, which is optionally substituted with from 1-4 **R^b**;

(iv) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^b**; or

(v) C₁₋₁₀ alkyl, which is optionally substituted with from 1-6 independently selected **R^a**;

each occurrence of **R³** is independently selected from the group consisting of -**L⁴**-**R⁴**, H and, **R^c**;

each occurrence of **L⁴** is independently selected from the group consisting of:

(i) a single bond;

(ii) N(H), N(**R^d**), or N(**R⁴**);

(iii) -N(H)S(O)₁₋₂- or -N(**R^d**)S(O)₁₋₂-;

(iv) -S(O)₁₋₂N(H)- or -S(O)₁₋₂N(**R^d**)-;

(v) -O-;

(vi) -S(O)₀₋₂-;

(vii) -C(O)NH- or -C(O)N(**R^d**);

(viii) -N(H)C(O)- or -N(**R^d**)C(O)-;

(ix) -C≡C-;

(x) -N(H)S(O)(=NH)-, -N(**R^d**)S(O)(=NH)-, -N(H)S(O)(=N**R^d**)-, or -N(**R^d**)S(O)(=N**R^d**)-

(xi) -S(O)(=NH)NH-, -S(O)(=N**R^d**)NH-, -S(O)(=NH)N**R^d**-, or -S(O)(=N**R^d**)N**R^d**-;

(xii) -S(O)(=NH)- or -S(O)(=N**R^d**); and

(xiii) -N(H)S(O)₁₋₂N(H)-, -N(**R^d**)S(O)₁₋₂N(H)-, -N(H)S(O)₁₋₂N(**R^d**)-, or -N(**R^d**)S(O)₁₋₂N(**R^d**)-;

each occurrence of **R⁴** is, independently:

(i) -(Y³)_p-Y⁴, wherein:

- **p** is 0 or 1;

- **Y³** is C₁₋₆ alkylene or C₁₋₆ alkenylene, each of which is optionally substituted with from 1-6 **R^a**; and
- **Y⁴** is:
 - (a) C₃₋₆ cycloalkyl, which is optionally substituted with from 1-4 **R^b**,
 - (b) C₆₋₁₀ aryl, which is optionally substituted with from 1-4 **R^c**;
 - (c) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**, or
 - (d) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^b**,

OR

(ii) C₁₋₁₀ alkyl, C₁₋₁₀ alkenyl, or C₁₋₁₀ alkynyl, each of which is optionally substituted with from 1-6 independently selected **R^a**;

each occurrence of **R^a** is independently selected from the group consisting of: -OH; -F; -Cl; -Br; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)O(C₁₋₄ alkyl); -C(=O)(C₁₋₄ alkyl); -C(=O)OH; -CON(R')(R''); -S(O)₁₋₂(NR'R''); -S(O)₁₋₂(C₁₋₄ alkyl); cyano, and C₃₋₆ cycloalkyl optionally substituted with from 1-4 independently selected C₁₋₄ alkyl;

each occurrence of **R^b** is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₄ haloalkyl; -OH; oxo; -F; -Cl; -Br; -NR^eR^f; C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)(C₁₋₄ alkyl); -C(=O)O(C₁₋₄ alkyl); -C(=O)OH; -C(=O)N(R')(R''); -S(O)₁₋₂(NR'R''); -S(O)₁₋₂(C₁₋₄ alkyl); cyano; and C₃₋₆ cycloalkyl optionally substituted with from 1-4 independently selected C₁₋₄ alkyl;

each occurrence of **R^c** is independently selected from the group consisting of:

(i) halo;

(ii) cyano;

(iii) C₁₋₆ alkyl;

- (iv) C₂₋₆ alkenyl;
- (v) C₂₋₆ alkynyl;
- (vi) C₁₋₄ haloalkyl;
- (vii) C₁₋₄ alkoxy;
- 5 (viii) C₁₋₄ haloalkoxy;
- (ix) -(C₀₋₃ alkylene)-C₃₋₆ cycloalkyl optionally substituted with from 1-4 independently selected C₁₋₄ alkyl;
- (x) -S(O)₁₋₂(C₁₋₄ alkyl);
- (xi) -NR^eR^f;
- 10 (xii) -OH;
- (xiii) -S(O)₁₋₂(NR'R'');
- (xiv) -C₁₋₄ thioalkoxy;
- (xv) -NO₂;
- (xvi) -C(=O)(C₁₋₄ alkyl);
- 15 (xvii) -C(=O)O(C₁₋₄ alkyl);
- (xviii) -C(=O)OH,
- (xix) -C(=O)N(R')(R''), and
- (xx) C₃₋₆ cycloalkoxy;

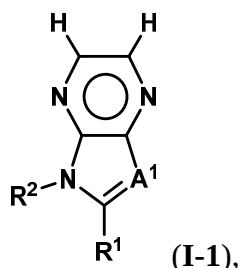
each occurrence of **R^c** is independently selected from the group consisting of:

- 20 (i) halo;
- (ii) cyano;
- (iii) -OH;
- (iv) -NO₂;
- (v) -C(=O)(C₁₋₄ alkyl);
- 25 (vi) -C(=O)O(C₁₋₄ alkyl);
- (vii) -C(=O)OH; and
- (viii) -NH₂;

R^d is selected from the group consisting of: C₁₋₆ alkyl; C₃₋₆ cycloalkyl; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CON(R')(R''); -S(O)₁₋₂(NR'R''); -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy;

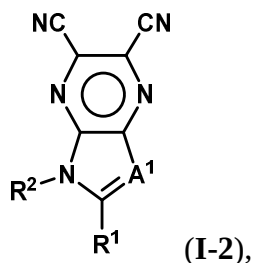
each occurrence of **R^e** and **R^f** is independently selected from the group consisting of: H; C₁₋₆ alkyl; C₃₋₆ cycloalkyl; -C(O)(C₁₋₄ alkyl); -C(O)O(C₁₋₄ alkyl); -CON(R')(R''); -S(O)₁₋₂(NR'R''); -S(O)₁₋₂(C₁₋₄ alkyl); -OH; and C₁₋₄ alkoxy; or **R^e** and **R^f** together with the nitrogen atom to which each is attached forms a ring including from 3-8 ring atoms, wherein the ring includes: (a) from 1-7 ring carbon atoms, each of which is substituted with from 1-2 substituents independently selected from H and C₁₋₃ alkyl; and (b) from 0-3 ring heteroatoms (in addition to the nitrogen atom attached to **R'** and **R''**), which are each independently selected from the group consisting of N(R^d), O, and S; and each occurrence of **R'** and **R''** is independently selected from the group consisting of: H and C₁₋₄ alkyl; or **R'** and **R''** together with the nitrogen atom to which each is attached forms a ring including from 3-8 ring atoms, wherein the ring includes: (a) from 1-7 ring carbon atoms, each of which is substituted with from 1-2 substituents independently selected from H and C₁₋₃ alkyl; and (b) from 0-3 ring heteroatoms (in addition to the nitrogen atom attached to **R'** and **R''**), which are each independently selected from the group consisting of N(**R^d**), O, and S;

provided that when the compound is of Formula (I-1):



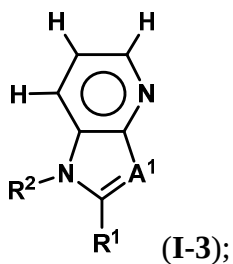
R¹ is other than unsubstituted phenyl, *para*-dimethylaminophenyl, *para*-aminosulfonylphenyl, and unsubstituted 4-pyridinyl;

when the compound is of Formula (I-2):

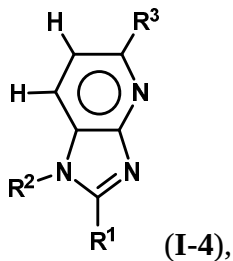


R¹ is other than unsubstituted phenyl;

provided that the compound is not of Formula (I-3):

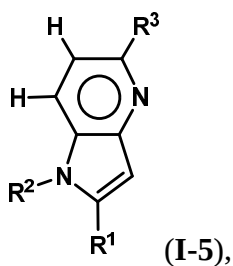


provided that when the compound is of Formula (I-4):



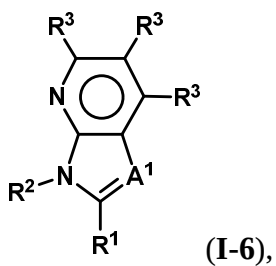
R¹ is other than *para*-fluorophenyl; and

5 provided that when the compound is of Formula (I-5):



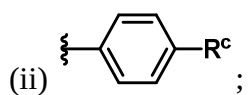
R³ is other than trifluoromethyl; and

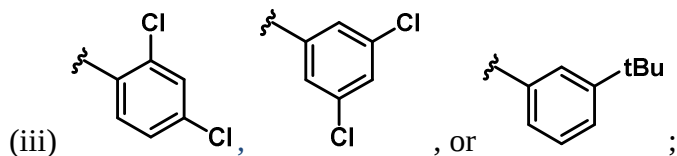
provided that when the compound is of Formula (I-6):



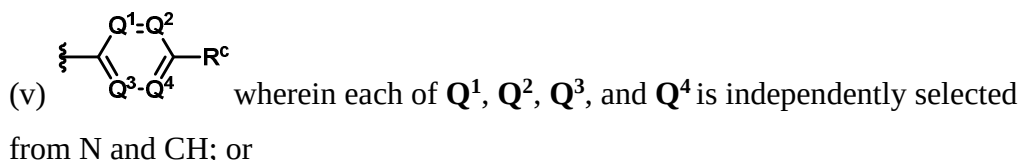
10 **R**² is other than:

(i) unsubstituted phenyl;





(iv) unsubstituted pyridinyl;



(vi) heteroaryl including from 9-10 ring atoms, wherein from 1-2 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-2 independently selected **R^c**.

In one example, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound or salt as disclosed herein and one or more pharmaceutically acceptable excipients.

In one example, methods for modulating (e.g., agonizing, partially agonizing,) APJ receptor activity are featured that include contacting the APJ receptor with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells, each independently comprising one or more APJ receptors with the chemical entity. Methods can also include *in vivo* methods. Such methods can include, e.g., administering the chemical entity to a subject (e.g., a human) having a disease, disorder, or condition in which

a decrease in APJ receptor activity (e.g., repressed or impaired APJ receptor signaling; e.g., repressed or impaired apelin-APJ receptor signaling) or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition (e.g., PAH; heart failure; type II diabetes; sepsis; renal failure; and systemic hypertension). *In vivo* methods include, but are not limited to modulating (e.g., decreasing) right ventricular afterload; modulating (e.g., decreasing) mean pulmonary artery pressure; modulating (e.g., increasing) insulin levels; and modulating (e.g., decreasing) glucose levels in a subject (e.g., a human).

In one aspect, the present disclosure refers to a method for modulating APJ receptor activity, the method comprising contacting the APJ receptor with a compound as disclosed herein.

In a further example, methods of treatment of a disease, disorder, or condition are featured, in a decrease in APJ receptor activity (e.g., repressed or impaired APJ receptor signaling; e.g., repressed or impaired apelin-APJ receptor signaling) or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same).

In another example, this disclosure features methods of treating a subject having a disease, disorder, or condition in which a decrease in APJ receptor activity (e.g., repressed or impaired APJ receptor signaling; e.g., repressed or impaired apelin-APJ receptor signaling) or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof or compositions containing the same) in an amount effective to treat the disease, disorder, or condition.

In a further example, methods of treatment are featured that include administering to a subject chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same). The methods include administering the chemical entity in an amount effective to treat a disease, disorder, or condition, wherein a decrease in APJ receptor activity (e.g., repressed or impaired APJ receptor signaling; e.g., repressed or impaired apelin-APJ

receptor signaling) or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition, thereby treating the disease, disorder, or condition.

In one aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a medicament for treating a disease, disorder, or condition, in which repressed or impaired APJ receptor signaling, or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition.

A non-limiting example of such diseases, disorders, and conditions is PAH. In some examples, the PAH is idiopathic. In other examples, the PAH is heritable PAH, toxin or drug-induced PAH; or a PAH associated with one or more of the following: congenital heart disease, connective tissue disorders (e.g., scleroderma, systemic lupus erythematosus, systemic sclerosis, Hashimoto's thyroiditis, Sjogren's Syndrome, and the antiphospholipid antibody syndrome), portal hypertension, BMPR2 mutations, Schistosomiasis, and HIV infection.

Another non-limiting example of such diseases, disorders, and conditions is cardiovascular disease, e.g., coronary heart disease and heart failure. In certain examples, the cardiovascular disease is heart failure; e.g., systolic heart failure, diastolic heart failure, diabetic heart failure and heart failure with preserved ejection fraction, cardiomyopathy, myocardial infarction, left ventricular dysfunction including left ventricular dysfunction after myocardial infarction, right ventricular dysfunction, right ventricular failure, cardiac hypertrophy, myocardial remodeling including myocardial remodeling after infarction or after cardiac surgery, and valvular heart diseases.

Still another non-limiting example of such diseases, disorders, and conditions is a metabolic disorder, such as metabolic syndrome; diabetes (e.g., type 2 diabetes); obesity; obesity-related disorders; impaired glucose tolerance; and insulin resistance.

Other non-limiting examples of such diseases, disorders, and conditions include sepsis, septic shock, renal failure, systemic hypertension, idiopathic pulmonary fibrosis (IPF), and systemic sclerosis.

Further non-limiting examples include coronary artery disease (CAD), non-CAD atherosclerotic conditions, including peripheral vascular disease (PVD), aortic atherosclerosis, and cerebral arteriosclerosis, diabetic retinopathy, ischemia-reperfusion injury, emphysema, radiation-induced organ and tissue injury, corpus luteum regression, scleroderma, systemic sclerosis, and diseases of immune dysregulation.

In one example, this disclosure features methods for identifying and/or selecting a subject (e.g., a human) likely to benefit from the methods described herein, as well as methods for determining whether a subject (e.g., a human) is responding to such methods. In certain examples, a biological sample, which may be, for example and without limitation, a breath, sputum, tissue, plasma or serum sample, urine, is obtained from the subject, and the level of a particular parameter in the sample is determined and compared to a control value. In some instances, the control value may be determined from one or more normal individuals not suffering from the disease, disorder, or conditions being treated. In other instances, the control value can also be determined from a sample previously obtained from the subject. Generally, higher (or elevated) levels of the measured parameter relative to a control value determined from a normal, non-diseased individual or population indicate that a subject will benefit from methods described herein. Lower levels generally indicate that a patient is responding to therapy or, for a subject not on such therapy, that the therapeutic methods may not be as beneficial for that subject.

In certain of the foregoing examples, the subject is suffering from, or at risk of suffering from PAH. Non-limiting, exemplary parameters related to PAH are delineated below.

In certain examples, the parameter is LTB4 level. For example, a baseline or reference value of LTB4 can be 100 pg/mL or greater, 200 pg/mL or greater, 300 pg/mL or greater, 400 pg/mL or greater, 500 pg/mL or greater, 600 pg/mL or greater, or 100 pg/mL or greater. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint LTB4 level of the subject decreases from the baseline or reference LTB4 level. For example, the endpoint LTB4 level of the subject decreases to 600 pg/mL or less, 500 pg/mL or less, 400 pg/mL or less, 300 pg/mL or less, 200 pg/mL or less, or 100 pg/mL or less. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint LTB4 level is 30 pg/mg of tissue or lower, 20 pg/mg of tissue or lower, 10 pg/mg of tissue or lower, 7.5 pg/mg of tissue or lower, or 5 pg/mg of tissue or lower. In other examples, the treatment provided is efficacious if, after treatment has started, the endpoint LTB4 level is lower than the baseline LTB4 level by 2-fold or more, 3-fold or more, 4-fold or more, or 5-fold or more.

In certain examples, the parameter is pulmonary vascular resistance (PVR). The baseline or reference PVR level can be 200 dynsec/cm⁵ or greater, 240 dynsec/cm⁵ or greater, 300 dynsec/cm⁵ or greater, 400 dynsec/cm⁵ or greater, 500 dynsec/cm⁵ or greater, 600 dynsec/cm⁵ or greater, 700 dynsec/cm⁵ or greater, or 800 dynsec/cm⁵ or greater. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint PVR level of the subject decreases from the baseline or reference PVR level by 70 dynsec/cm⁵ or more, 100 dynsec/cm⁵ or more, 130 dynsec/cm⁵ or more, or 160 dynsec/cm⁵ or more.

In certain examples, the parameter is pulmonary arterial pressure (PAP). The baseline or reference PAP level can be 20 mmHg or greater, 25 mmHg or greater, 30 mmHg or greater, 35 mmHg or greater, 40 mmHg or greater, 45 mmHg or greater, 50 mmHg or greater, 60 mmHg or greater, or 70 mmHg or greater. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint PAP level of the subject decreases from the baseline or reference PAP level by 0.5 mmHg or more, 1 mmHg or more, 1.5 mmHg or more, 5 mmHg or more, 10 mmHg or more, 20 mmHg or more, 30 mmHg or more, 40 mmHg or more, or 50 mmHg. In certain examples, the subject exhibits a mean pulmonary artery pressure of greater than 25 mmHg.

In certain examples, the parameter is cardiac index (CI). A baseline or reference CI level can be 5 L/min/m.sup.2 or lower, 2.5 L/min/m.sup.2 or lower, 2 L/min/m.sup.2 or lower, 1.5 L/min/m.sup.2 or lower, or 1 L/min/m.sup.2 or lower. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint CI level increases from the baseline or reference CI level by 0.1 or more, 0.2 or more, 0.3 or more, 0.4 or more, 0.5 or more, 1 or more, or 2 or more.

In certain examples, the parameter is pulmonary capillary wedge pressure (PCWP). A baseline or reference PCWP level can be 36 mmHg or less, 24 mmHg or less, 18 mmHg or less, 10 mmHg, or 5 mmHg or less. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint PCWP level increases from the baseline or reference PCWP level by 0.2 mmHg or more, 0.3 mmHg or more, 0.4 mmHg or more, 0.5 mmHg or more, 0.6 mmHg or more, 1 mmHg or more, or 5 mmHg or more.

In certain examples, the parameter is right atrial pressure (RAP). A baseline or reference RAP level can be 4 mmHg or more, 6 mmHg or more, 8 mmHg or more, 10 mmHg or more, 12 mmHg or more, 16 mmHg or more, 20 mmHg or more, or 25 mmHg or more. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint RAP level of the subject decreases from the baseline or reference RAP level by 5 mmHg or more, 2.5 mmHg or more, 1 mmHg or more, 0.5 mmHg or more, or 0.2 mmHg or more.

In certain examples, the parameter is the six-minute walk distance (6 MWD). A baseline or reference 6 MWD can be 50 m or less, 100 m or less, 200 m or less, 300 m or less, 400 m or less, or 500 m or less. In certain examples, the treatment provided is efficacious if after treatment has started, the endpoint 6 MWD of the subject increases from the baseline or reference 6 MWD by 10 m or more, 15 m or more, 20 m or more, 25 m or more, 30 m or more, or 50 m or more. Alternatively or in addition, treatment provided in the disclosure is efficacious if, after treatment has started, the endpoint 6 MWD of the subject increases by 3% or more, 4% or more, 5% or more, 10% or more, or 20% or more of the baseline level.

In certain examples, the parameter is brain natriuretic peptide (BNP) level. A baseline or reference BNP level can be 60 pg/mL or higher, 80 pg/mL or higher, 100 pg/mL or higher, 120 pg/mL or higher, 140 pg/mL or higher, 200 pg/mL or higher, 500 pg/mL or higher, or 1000 pg/mL or higher. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint BNP level of the subject decreases from the baseline or reference BNP level. For example, the endpoint BNP level of the subject can decrease by 1 pg/mL or more, 2 pg/mL or more, 5 pg/mL or more, 10 pg/mL or more, 20 pg/mL or more, 100 pg/mL or more, 500 pg/mL or more, or 1000 pg/mL or more.

In certain examples, the parameter is atrial natriuretic peptide (ANP) level. A baseline or reference ANP level can be 60 pg/mL or higher, 80 pg/mL or higher, 100 pg/mL or higher, 120 pg/mL or higher, 140 pg/mL or higher, 200 pg/mL or higher, 500 pg/mL or higher, or 1000 pg/mL or higher. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint ANP level of the subject decreases

from the baseline or reference ANP level. For example, the endpoint ANP level of the subject can decrease by 1 pg/mL or more, 2 pg/mL or more, 5 pg/mL or more, 10 pg/mL or more, 20 pg/mL or more, 100 pg/mL or more, 500 pg/mL or more, or 1000 pg/mL or more.

5 In certain examples, the parameter is Diffusion of lung capacity (DLCO), or diffusion capacity of CO, can also be used in the methods as a parameter to determine efficacy. A baseline or reference DLCO can be 90% or less, 80% or less, 70% or less, 50% or less, 45% or less, or 40% or less. In certain examples, the treatment provided is efficacious if, after treatment has started, the endpoint DLCO is increased from the
10 baseline level. For example, the endpoint DLCO can be increased from the baseline or reference DLCO by 1% or more, 5% or more, 10% or more, 15% or more, 20% or more, or 50% or more.

 In another example, this disclosure features methods for reducing the risk of right
15 ventricular failure in a subject in need of such reducing, the method comprising administering to the subject an effective amount of a chemical entity described herein.

 The methods described herein can further include treating one or more conditions that are associated, co-morbid or sequela with any one or more of the conditions described herein.

20 For example, the methods can further include treating one or more conditions that are associated, co-morbid or sequela with PAH, e.g., coronary heart disease or heart failure. In certain examples, the cardiovascular disease is heart failure, e.g., systolic heart failure, diastolic heart failure, diabetic heart failure and heart failure with preserved ejection fraction, cardiomyopathy, myocardial infarction, left ventricular dysfunction
25 including left ventricular dysfunction after myocardial infarction, right ventricular dysfunction , right ventricular failure, cardiac hypertrophy, myocardial remodeling including myocardial remodeling after infarction or after cardiac surgery, and valvular heart diseases.

 As another example, the methods can further include treating one or more
30 conditions that are co-morbid or sequela with diabetes (e.g., type 2 diabetes), such as

obesity, obesity-related disorders, metabolic syndrome, impaired glucose tolerance; insulin resistance; cardiovascular risk factors. (e.g., coronary artery disease, peripheral artery disease, cerebrovascular disease, hypertension, and risk factors related to unmanaged cholesterol and/or lipid levels, and/or inflammation), retinopathy, nephropathy, neuropathy, NASH, bone fracture and cognitive dysfunction.

The methods can further include administering one or more other therapeutic agents (e.g., in combination with a chemical entity described herein).

Examples can include one of more of the following advantageous properties.

Apelin peptide is labile; as such, only acute pharmacodynamics effect of apelin peptide is observable. In some examples, the compounds described herein exhibit relatively high metabolic stability to allow observations of non-acute pharmacodynamics effect.

In some examples, the compounds described herein can lead to reduced atrial pressure in addition to enhancing cardiac output.

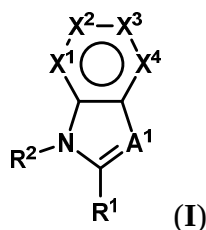
In some examples, the compounds described herein can selectively activate the G-protein pathway through APJ receptor, thereby reducing tachyphylaxis often associated with dosing potent agonists. As such, in certain examples, compounds described herein can reduce arrestin-associated cardiac hypertrophy.

In some examples, the compounds described herein can exhibit pleiotropic properties (e.g., inodilator activity, cardio-renal protection, and control of fluid homeostasis).

Other examples include those described in the Detailed Description and/or in the claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

A^1 is CH or N;

each of X^1 , X^2 , X^3 , and X^4 is independently selected from the group consisting of N and CR^3 ;

R^1 is:

(i) $-(Y^1)_n-Y^2$, wherein:

- n is 0 or 1;
- Y^1 is C_{1-6} alkylene, which is optionally substituted with from 1-6 R^a ; and
- Y^2 is:
 - (a) C_{3-10} cycloalkyl, which is optionally substituted with from 1-4 R^b ;
 - (b) C_{6-10} aryl, which is optionally substituted with from 1-4 R^c ;
 - (c) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected R^c , or
 - (d) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected R^b ,

OR

(ii) $-Z^1-Z^2-Z^3$, wherein:

- Z^1 is C_{1-3} alkylene, which is optionally substituted with from 1-4 R^a ;
- Z^2 is $-N(H)-$, $-N(R^d)-$, $-O-$, or $-S-$; and
- Z^3 is C_{2-7} alkyl, which is optionally substituted with from 1-4 R^a ;

OR

(iii) C_{3-10} alkyl, optionally substituted with from 1-6 independently selected R^a ;

OR

(iv) $-Z^4-Z^5-Z^6-Y^2$ wherein:

- Z^4 is C_{1-3} alkylene, which is optionally substituted with from 1-4 R^a ;
- Z^5 is $-N(H)-$, $-N(R^d)-$, $-O-$, or $-S-$;
- Z^6 is C_{1-4} alkylene, which is optionally substituted with from 1-4 R^a ; and
- Y^2 is as defined above;

R^2 is:

(i) C_{6-10} aryl, which is optionally further substituted with from 1-4 R^c ;

(ii) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected R^c ;

(iii) C_{3-10} cycloalkyl, which is optionally substituted with from 1-4 R^b ;

(iv) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected R^b ; or

(v) C_{1-10} alkyl, which is optionally substituted with from 1-6 independently selected R^a ;

each occurrence of R^3 is independently selected from the group consisting of $-L^4-R^4$, H and, R^c ;

each occurrence of $\mathbf{L}^4$ is independently selected from the group consisting of:

- (i) a single bond;
- (ii) N(H) , $\text{N(R}^{\text{d}})$, or $\text{N(R}^4)$;
- (iii) $-\text{N(H)S(O)}_{1-2}-$ or $-\text{N(R}^{\text{d}})\text{S(O)}_{1-2}-$;
- (iv) $-\text{S(O)}_{1-2}\text{N(H)}-$ or $-\text{S(O)}_{1-2}\text{N(R}^{\text{d}})-$;
- (v) $-\text{O}-$;
- (vi) $-\text{S(O)}_{0-2}-$;
- (vii) $-\text{C(O)NH}-$ or $-\text{C(O)N(R}^{\text{d}})-$;
- (viii) $-\text{N(H)C(O)}-$ or $-\text{N(R}^{\text{d}})\text{C(O)}-$;
- (ix) $-\text{C}\equiv\text{C}$;
- (x) $-\text{N(H)S(O)(=NH)}-$, $-\text{N(R}^{\text{d}})\text{S(O)(=NH)}$, $-\text{N(H)S(O)(=NR}^{\text{d}})-$, or $-\text{N(R}^{\text{d}})\text{S(O)(=NR}^{\text{d}})-$;
- (xi) $-\text{S(O)(=NH)NH}-$, $-\text{S(O)(=NR}^{\text{d}})\text{NH}-$, $-\text{S(O)(=NH)NR}^{\text{d}}-$, or $-\text{S(O)(=NR}^{\text{d}})\text{NR}^{\text{d}}-$;
- (xii) $-\text{S(O)(=NH)}-$ or $-\text{S(O)(=NR}^{\text{d}})-$; and
- (xiii) $-\text{N(H)S(O)}_{1-2}\text{N(H)}-$, $-\text{N(R}^{\text{d}})\text{S(O)}_{1-2}\text{N(H)}-$, $-\text{N(H)S(O)}_{1-2}\text{N(R}^{\text{d}})-$, or $-\text{N(R}^{\text{d}})\text{S(O)}_{1-2}\text{N(R}^{\text{d}})-$;

each occurrence of $\mathbf{R}^4$ is, independently:

- (i) $-(\mathbf{Y}^3)_p-\mathbf{Y}^4$, wherein:
 - p is 0 or 1;
 - $\mathbf{Y}^3$ is C_{1-6} alkylene or C_{1-6} alkenylene, each of which is optionally substituted with from 1-6 $\mathbf{R}^{\text{a}}$; and
 - $\mathbf{Y}^4$ is:
 - (a) C_{3-6} cycloalkyl, which is optionally substituted with from 1-4 $\mathbf{R}^{\text{b}}$,
 - (b) C_{6-10} aryl, which is optionally substituted with from 1-4 $\mathbf{R}^{\text{c}}$;
 - (c) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H) , $\text{N(R}^{\text{d}})$, O, and S, and wherein one or

more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected $\mathbf{R}^c$, or

(d) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected $\mathbf{R}^b$,

OR

(ii) C_{1-10} alkyl, C_{1-10} alkenyl, or C_{1-10} alkynyl, each of which is optionally substituted with from 1-6 independently selected $\mathbf{R}^a$;

each occurrence of $\mathbf{R}^a$ is independently selected from the group consisting of: $-\text{OH}$; $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{NR}^e\text{R}^f$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-\text{C}(=\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(=\text{O})(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(=\text{O})\text{OH}$; $-\text{CON}(\text{R}')(\text{R}'')$; $-\text{S}(\text{O})_{1-2}(\text{NR}'\text{R}'')$; $-\text{S}(\text{O})_{1-2}(\text{C}_{1-4} \text{ alkyl})$; cyano, and C_{3-6} cycloalkyl optionally substituted with from 1-4 independently selected C_{1-4} alkyl;

each occurrence of $\mathbf{R}^b$ is independently selected from the group consisting of: C_{1-6} alkyl; C_{1-4} haloalkyl; $-\text{OH}$; oxo; $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{NR}^e\text{R}^f$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-\text{C}(=\text{O})(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(=\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$; $-\text{C}(=\text{O})\text{OH}$; $-\text{C}(=\text{O})\text{N}(\text{R}')(\text{R}'')$; $-\text{S}(\text{O})_{1-2}(\text{NR}'\text{R}'')$; $-\text{S}(\text{O})_{1-2}(\text{C}_{1-4} \text{ alkyl})$; cyano; and C_{3-6} cycloalkyl optionally substituted with from 1-4 independently selected C_{1-4} alkyl;

each occurrence of $\mathbf{R}^c$ is independently selected from the group consisting of:

- (i) halo;
- (ii) cyano;
- (iii) C_{1-6} alkyl;
- (iv) C_{2-6} alkenyl;
- (v) C_{2-6} alkynyl;
- (vi) C_{1-4} haloalkyl;
- (vii) C_{1-4} alkoxy;
- (viii) C_{1-4} haloalkoxy;

- (ix) $-(C_{0-3} \text{ alkylene})-C_{3-6} \text{ cycloalkyl}$ optionally substituted with from 1-4 independently selected C_{1-4} alkyl;
- (x) $-S(O)_{1-2}(C_{1-4} \text{ alkyl})$;
- (xi) $-NR^eR^f$;
- (xii) $-OH$;
- (xiii) $-S(O)_{1-2}(NR'R'')$;
- (xiv) $-C_{1-4} \text{ thioalkoxy}$;
- (xv) $-NO_2$;
- (xvi) $-C(=O)(C_{1-4} \text{ alkyl})$;
- (xvii) $-C(=O)O(C_{1-4} \text{ alkyl})$;
- (xviii) $-C(=O)OH$,
- (xix) $-C(=O)N(R')(R'')$, and
- (xx) $C_{3-6} \text{ cycloalkoxy}$;

each occurrence of R^c is independently selected from the group consisting of:

- (i) halo;
- (ii) cyano;
- (iii) $-OH$;
- (iv) $-NO_2$;
- (v) $-C(=O)(C_{1-4} \text{ alkyl})$;
- (vi) $-C(=O)O(C_{1-4} \text{ alkyl})$;
- (vii) $-C(=O)OH$; and
- (viii) $-NH_2$;

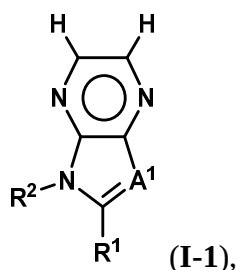
R^d is selected from the group consisting of: C_{1-6} alkyl; C_{3-6} cycloalkyl; $-C(O)(C_{1-4} \text{ alkyl})$; $-C(O)O(C_{1-4} \text{ alkyl})$; $-CON(R')(R'')$; $-S(O)_{1-2}(NR'R'')$; $-S(O)_{1-2}(C_{1-4} \text{ alkyl})$; $-OH$; and $C_{1-4} \text{ alkoxy}$;

each occurrence of R^e and R^f is independently selected from the group consisting of: H; C_{1-6} alkyl; C_{3-6} cycloalkyl; $-C(O)(C_{1-4} \text{ alkyl})$; $-C(O)O(C_{1-4} \text{ alkyl})$; $-CON(R')(R'')$; $-S(O)_{1-2}(NR'R'')$; $-S(O)_{1-2}(C_{1-4} \text{ alkyl})$; $-OH$; and $C_{1-4} \text{ alkoxy}$; or R^e and R^f together with

the nitrogen atom to which each is attached forms a ring including from 3-8 ring atoms, wherein the ring includes: **(a)** from 1-7 ring carbon atoms, each of which is substituted with from 1-2 substituents independently selected from H and C₁₋₃ alkyl; and **(b)** from 0-3 ring heteroatoms (in addition to the nitrogen atom attached to **R'** and **R''**), which are each independently selected from the group consisting of N(R^d), O, and S; and

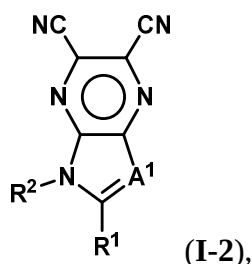
each occurrence of **R'** and **R''** is independently selected from the group consisting of: H and C₁₋₄ alkyl; or **R'** and **R''** together with the nitrogen atom to which each is attached forms a ring including from 3-8 ring atoms, wherein the ring includes: **(a)** from 1-7 ring carbon atoms, each of which is substituted with from 1-2 substituents independently selected from H and C₁₋₃ alkyl; and **(b)** from 0-3 ring heteroatoms (in addition to the nitrogen atom attached to **R'** and **R''**), which are each independently selected from the group consisting of N(R^d), O, and S;

provided that when the compound is of Formula **(I-1)**:



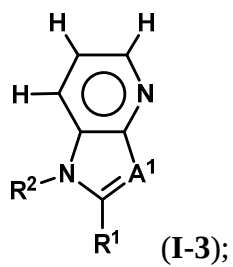
R¹ is other than unsubstituted phenyl, *para*-dimethylaminophenyl, *para*-aminosulfonylphenyl, and unsubstituted 4-pyridinyl;

when the compound is of Formula **(I-2)**:

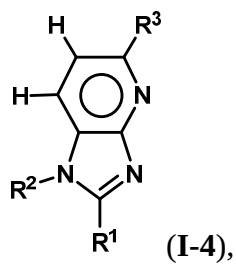


R¹ is other than unsubstituted phenyl;

provided that the compound is not of Formula **(I-3)**:

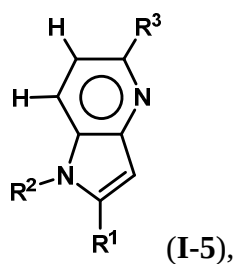


provided that when the compound is of Formula (I-4):



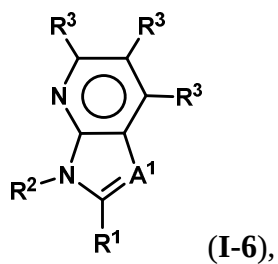
R¹ is other than *para*-fluorophenyl; and

provided that when the compound is of Formula (I-5):



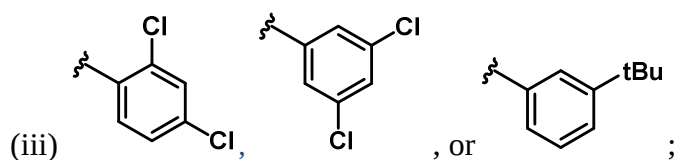
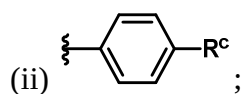
R³ is other than trifluoromethyl; and

provided that when the compound is of Formula (I-6):

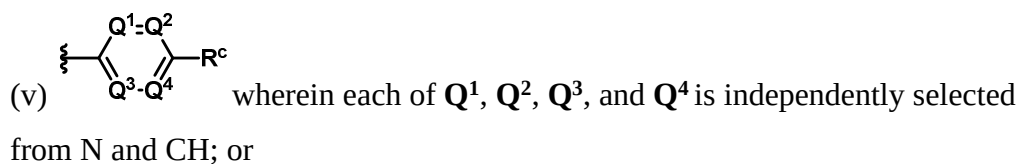


R² is other than:

(i) unsubstituted phenyl;

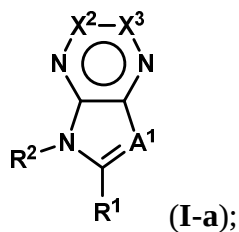


(iv) unsubstituted pyridinyl;



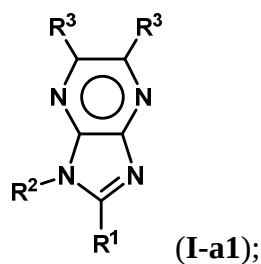
(vi) heteroaryl including from 9-10 ring atoms, wherein from 1-2 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-2 independently selected **R^c**.

2. The compound of claim 1, wherein the compound is of Formula (**I-a**):



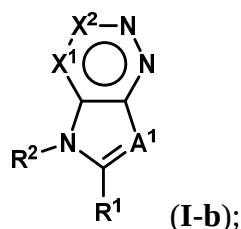
or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1-2, wherein the compound is of Formula (**I-a1**):



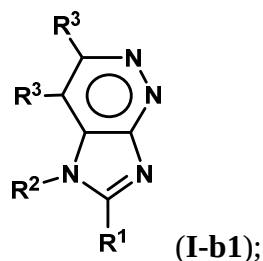
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of Formula **(I-b)**:



or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 and 4, wherein the compound is of Formula **(I-b1)**:



or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-5, wherein **R¹** is $-(Y^1)_n-Y^2$.

7. The compound of any one of claims 1-6, wherein **n** is 0.

8. The compound of any one of claims 1-7, wherein **Y²** is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**Rᵈ**), O, and S, and

wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**.

9. The compound of any one of claims 1-8, wherein **Y²** is heteroaryl including 6 ring atoms, wherein from 1-2 ring atoms are N, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**.

10. The compound of claim 9, wherein **Y²** is pyridyl (e.g., 2-pyridyl or 6-pyridyl), wherein one or more of the ring carbon atoms are optionally substituted with from 1-4 independently selected **R^c**.

11. The compound of any one of claims 8-10, wherein each occurrence of **R^c** is independently selected from the group consisting of:

(iii) C₁₋₆ alkyl;

(iv) C₂₋₆ alkenyl;

(v) C₂₋₆ alkynyl;

(vi) C₁₋₄ haloalkyl;

(vii) C₁₋₄ alkoxy;

(viii) C₁₋₄ haloalkoxy;

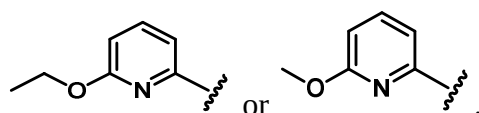
(ix) -(C₀₋₃ alkylene)-C₃₋₆ cycloalkyl optionally substituted with from 1-4

independently selected C₁₋₄ alkyl;

(xiv) -C₁₋₄ thioalkoxy; and

(xx) C₃₋₆ cycloalkoxy.

12. The compound of any one of claims 1-11, wherein **R¹** is:



13. The compound of any one of claims 1-12, wherein **R**² is C₆₋₁₀ aryl, which is optionally substituted with from 1-4 **R**^c.

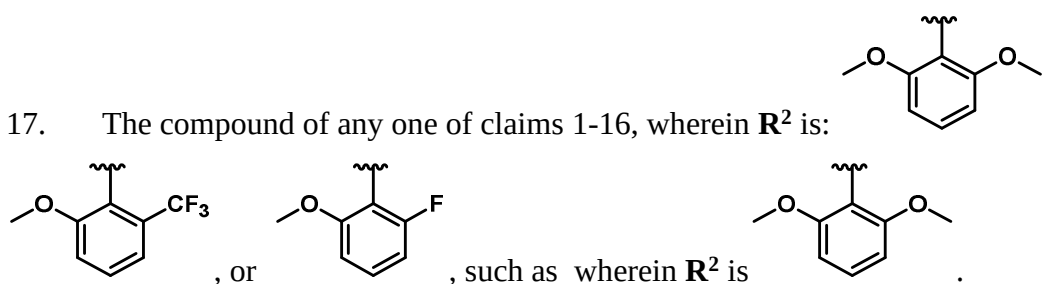
14. The compound of any one of claims 1-13, wherein **R**² is phenyl, which is optionally substituted with from 1-4 **R**^c.

15. The compound of any one of claims 1-14, wherein **R**² is phenyl, which is optionally substituted with 2 **R**^c.

16. The compound of any one of claims 13-15, wherein each occurrence of **R**^c is independently selected from the group consisting of:

- (i) halo (e.g., F);
- (vi) C₁₋₄ haloalkyl (e.g., CF₃);
- (vii) C₁₋₄ alkoxy;
- (viii) C₁₋₄ haloalkoxy; and
- (xiv) -C₁₋₄ thioalkoxy.

17. The compound of any one of claims 1-16, wherein **R**² is:



18. The compound of any one of claims 1-17, wherein one occurrence of **R**³ is – **L**⁴-**R**⁴.

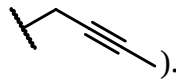
19. The compound of any one of claims 1-18, wherein one occurrence of **R**³ is – **L**⁴-**R**⁴; and each of the remaining occurrences of **R**³ is independently selected from the group consisting of H and **R**^c (e.g., **R**^c can be halo, e.g., Br or Cl; or **R**^c can be NH₂).

20. The compound of any one of claims 1-19, wherein one occurrence of $\mathbf{R}^3$ is $-\mathbf{L}^4-\mathbf{R}^4$, and each of the remaining occurrences of $\mathbf{R}^3$ is H.
21. The compound of any one of claims 1-17, wherein two occurrences of $\mathbf{R}^3$ are independently selected $-\mathbf{L}^4-\mathbf{R}^4$.
22. The compound of any one of claims 1-17 and 21, wherein any remaining occurrence of $\mathbf{R}^3$ is selected from the group consisting of H and $\mathbf{R}^{c'}$.
23. The compound of any one of claims 1-17 and 21-22, wherein any remaining occurrence of $\mathbf{R}^3$ is H.
24. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $-\text{N(H)S(O)}_{1-2}-$ or $-\text{N(R}^d\text{)S(O)}_{1-2}$ (e.g., $\text{N(C}_{1-3}\text{ alkyl)S(O)}_2$).
25. The compound of any one of claims 1-24, wherein $\mathbf{L}^4$ is $-\text{N(H)S(O)}_2-$.
26. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $-\text{N(H)C(O)}-$ or $-\text{N(R}^d\text{)C(O)}$.
27. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $-\text{C(O)NH}-$ or $-\text{C(O)N(R}^d\text{)}-$.
28. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $-\text{N(H)}-$, $-\text{N(R}^d\text{)}-$, or $-\text{N(R}^4\text{)}-$.
29. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is a single bond.
30. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $\text{C}\equiv\text{C}$.
31. The compound of any one of claims 1-23, wherein $\mathbf{L}^4$ is $-\text{O}-$.

32. The compound of any one of claims 1-23, wherein L^4 is selected from the group consisting of: $-N(H)S(O)_{1-2}N(H)-$, $-N(R^d)S(O)_{1-2}N(H)-$, $-N(H)S(O)_{1-2}N(R^d)-$, and $-N(R^d)S(O)_{1-2}N(R^d)-$.
33. The compound of any one of claims 1-32, wherein R^4 is $-(Y^3)_p-Y^4$.
34. The compound of any one of claims 1-33, wherein Y^3 is C_{1-3} alkylene.
35. The compound of any one of claims 1-34, wherein Y^4 is C_{6-10} aryl, which is optionally substituted with from 1-4 R^c .
36. The compound of any one of claims 1-34, wherein Y^4 is C_{3-6} (e.g., C_{3-4} or C_6) cycloalkyl, which is optionally substituted with from 1-4 R^b .
37. The compound of any one of claims 1-34, wherein Y^4 is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and S, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected R^c .
38. The compound of any one of claims 1-34, wherein Y^4 is heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, and O, and wherein one or more of the heterocyclyl ring carbon atoms are optionally substituted with from 1-4 independently selected R^b .
39. The compound of any one of claims 1-32, wherein R^4 is C_{1-10} alkyl, optionally substituted with from 1-6 independently selected R^a .
40. The compound of any one of claims 1-32 and 39, wherein R^4 is C_{1-6} alkyl, optionally substituted with from 1-6 independently selected R^a .

41. The compound of any one of claims 1-32, wherein **R**⁴ is C₂₋₁₀ (e.g., C₂₋₄) alkynyl, which is optionally substituted with from 1-6 (e.g., from 1-3) independently

selected **R**^a (e.g., unsubstituted C₂₋₄ alkynyl such as



42. The compound of any one of claims 1-32, wherein **R**⁴ is C₂₋₁₀ (e.g., C₂₋₄) alkenyl, which is optionally substituted with from 1-6 (e.g., from 1-3) independently selected **R**^a (e.g., unsubstituted C₂₋₄ alkenyl such as vinyl).

43. The compound of any one of claims 1-23, wherein:

-**L**⁴ is selected from the group consisting of -N(H)S(O)₂-, C≡C, a single bond, -C(O)N(H)-, -N(H)-, -N(**R**⁴)-, -N(**R**^d)-, and -N(H)C(O)-; and

R⁴ is selected from the group consisting of:

(i) C₁₋₆ alkyl optionally substituted with 1-2 **R**^a; and

(ii) -(Y³)_p-Y⁴.

44. The compound of any one of claims 1-23 and 43, wherein:

-**L**⁴ is selected from the group consisting of -N(H)S(O)₂-, a single bond, -NH-, -N(**R**⁴)-, and -N(H)C(O)-; and

R⁴ is selected from the group consisting of:

(i) C₁₋₆ alkyl optionally substituted with 1-2 **R**^a; and

(ii) -(Y³)_p-Y⁴.

45. The compound of any one of claims 1-23, wherein:

-**L**⁴ is selected from the group consisting of -N(H)S(O)₂-, -N(H)S(O)₂N(H)-, -N(H)S(O)₂N(**R**^d)-, C≡C, a single bond, -C(O)N(H)-, -N(H)-, -N(**R**⁴)-, -N(**R**^d)-, and -N(H)C(O)-; and

R⁴ is selected from the group consisting of:

(i) C₁₋₆ alkyl optionally substituted with 1-2 **R**^a; and

(ii) -(Y³)_p-Y⁴; and

(iii) C₂₋₁₀ alkenyl or C₂₋₁₀ alkynyl, each of which is optionally substituted with from 1-3 independently selected **R^a**.

46. The compound of any one of claims 1-23 and 45, wherein:

-L⁴ is selected from the group consisting of **-N(H)S(O)₂-**, **-N(H)S(O)₂N(H)-**, and **-N(H)S(O)₂N(**R^d**)-**; and

R⁴ is selected from the group consisting of:

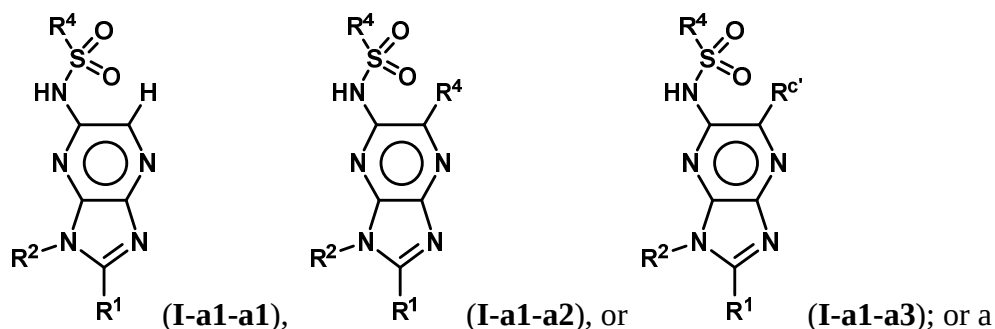
(i) C₁₋₆ alkyl optionally substituted with 1-2 **R^a**;

(ii) **-(Y³)_p-Y⁴**; and

(iii) C₂₋₁₀ alkenyl or C₂₋₁₀ alkynyl, each of which is optionally substituted with from 1-3 independently selected **R^a**.

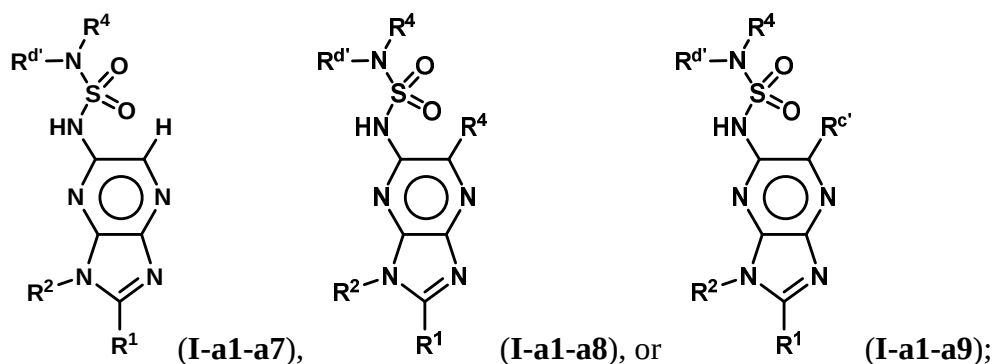
47. The compound of any one of claims 43-46, wherein **-L⁴** is **-N(H)S(O)₂-**.

48. The compound of claim 1-3, wherein the compound is of Formula **(I-a1-a1)**, **(I-a1-a2)**, or **(I-a1-a3)**:



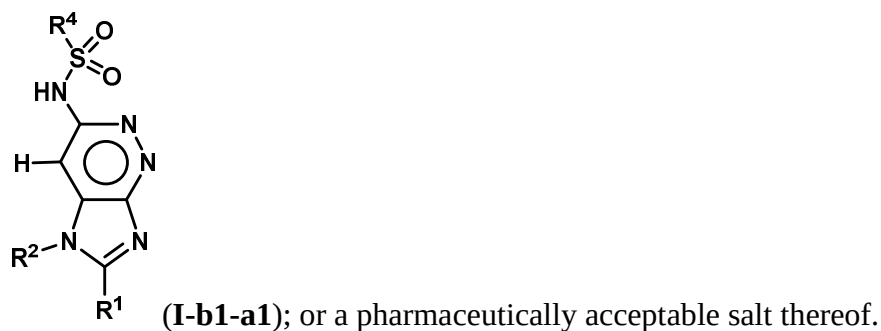
pharmaceutically acceptable salt thereof.

49. The compound of claim 1-3, wherein the compound is of Formula **(I-a1-a7)**, **(I-a1-a8)**, or **(I-a1-a9)**:

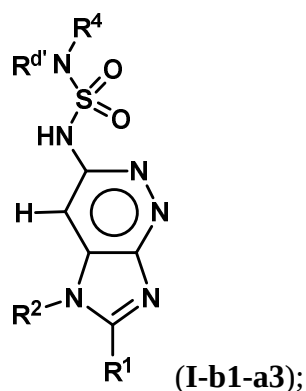


wherein $R^{d'}$ is H or R^d (e.g., H or C_{1-3} alkyl); or a pharmaceutically acceptable salt thereof.

50. The compound of any one of claims 1, 4, and 5, wherein the compound is of Formula (I-b1-a1):



51. The compound of any one of claims 1, 4 and 5, wherein the compound is of Formula (I-b1-a3):



wherein $R^{d'}$ is H or R^d (e.g., H or C_{1-3} alkyl); or a pharmaceutically acceptable salt thereof.

52. The compound of any one of the preceding claims, wherein **R**⁴ is selected from the group consisting of:

- (i) C₁₋₁₀ alkyl, optionally substituted with from 1-6 independently selected **R**^a;
- (ii) -(**Y**³)_p-**Y**⁴; and
- (iii) C₂₋₁₀ alkenyl or C₂₋₁₀ alkynyl, each of which is optionally substituted with from 1-3 independently selected **R**^a.

53. The compound of any one of the preceding claims, wherein:

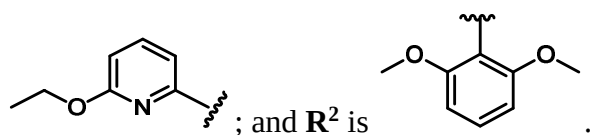
R¹ is -(**Y**¹)_n-**Y**²; and

R² is C₆₋₁₀ aryl, which is optionally substituted with from 1-4 **R**^c.

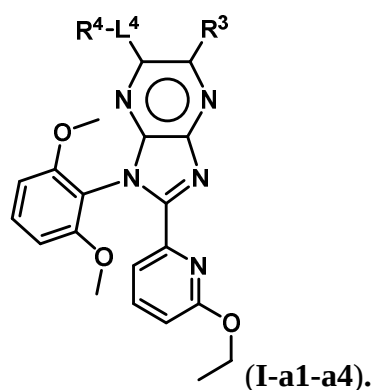
54. The compound of claim 53, wherein **Y**² is heteroaryl including 6 ring atoms, wherein from 1-2 ring atoms are N, and wherein one or more of the heteroaryl ring carbon atoms are optionally substituted with from 1-4 independently selected **R**^c.

55. The compound of any one of claims 53 and 54, wherein **R**² is phenyl, which is optionally substituted with from 1-4 **R**^c.

56. The compound of any one of the preceding claims, wherein **R**¹ is



57. The compound of any one of the preceding claims, wherein the compound is of Formula **(I-a1-a4)**:

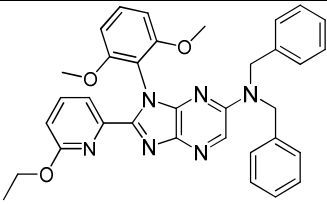
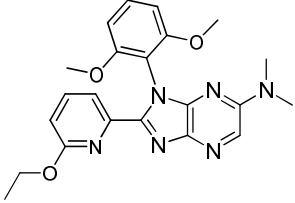
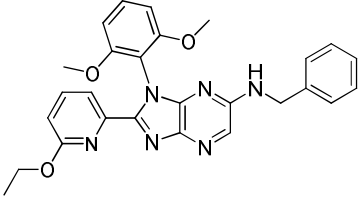
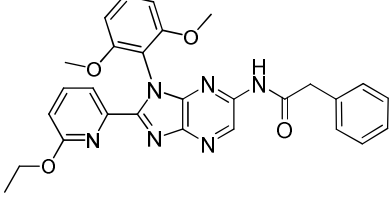
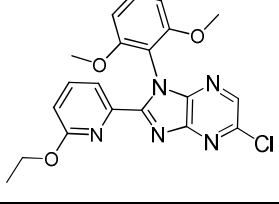
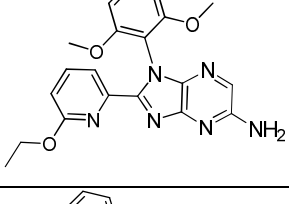
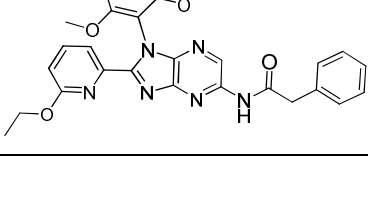


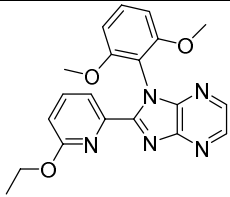
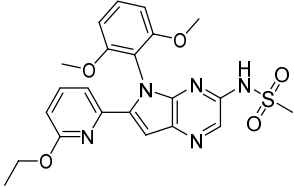
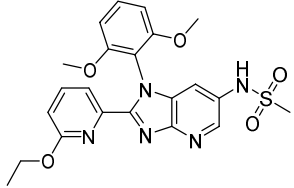
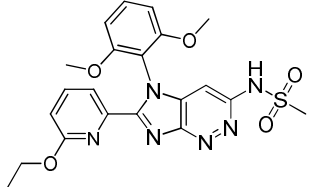
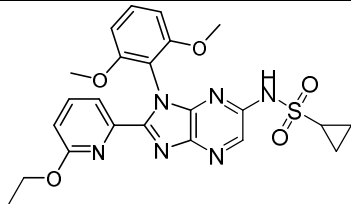
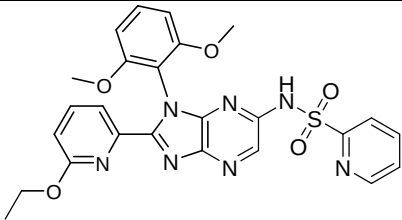
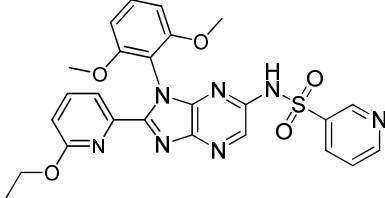
58. The compound of claim 57, wherein L^4 is $NHS(O)_2$.

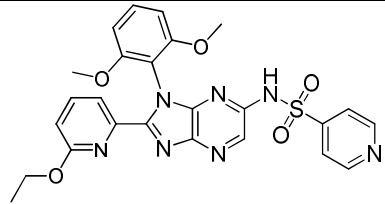
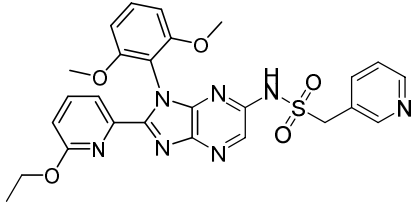
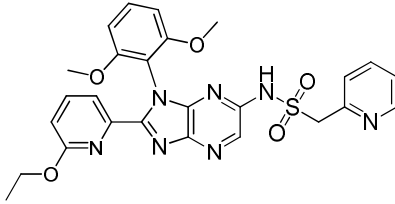
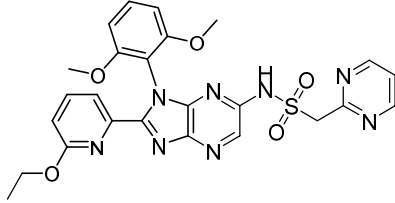
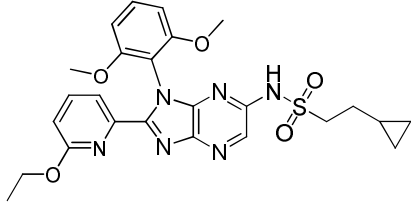
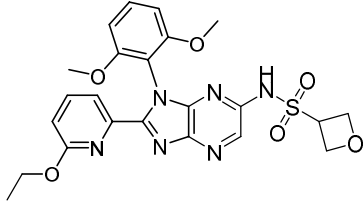
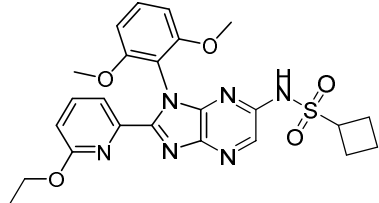
59. The compound of claim 1, wherein the compound is selected from the group consisting of those in the table below:

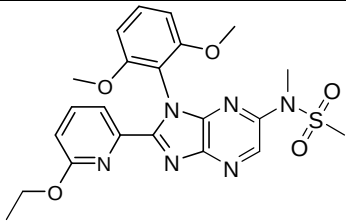
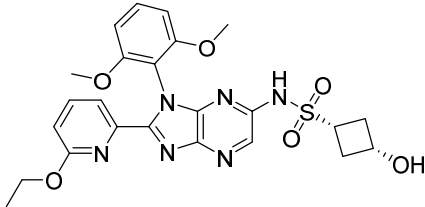
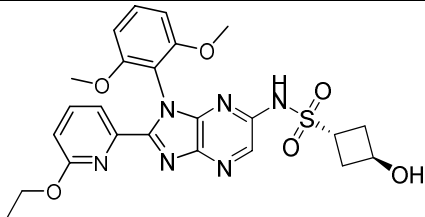
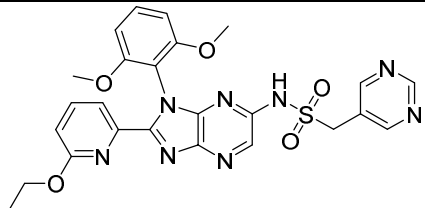
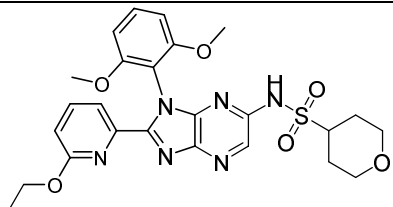
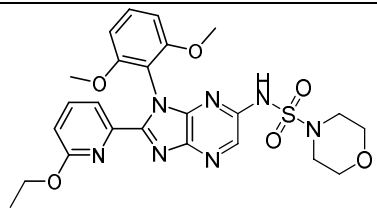
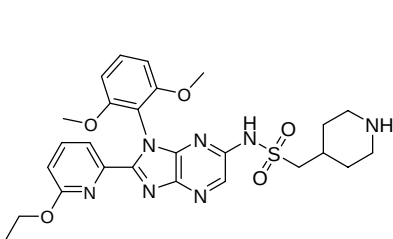
Exempl e #	Structure	IUPAC Name
1		6-bromo-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazine
2		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
3		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-phenylmethanesulfonamide

4		1-cyclopropyl-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
5		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)benzenesulfonamide
6		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-6-(phenylethynyl)-1H-imidazo[4,5-b]pyrazine
7		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-6-phenethyl-1H-imidazo[4,5-b]pyrazine
8		N-Benzyl-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazine-6-carboxamide
9		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-N-methyl-1H-imidazo[4,5-b]pyrazin-6-amine
10		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-amine

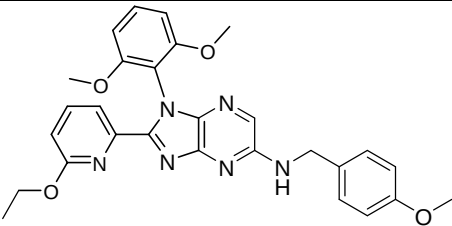
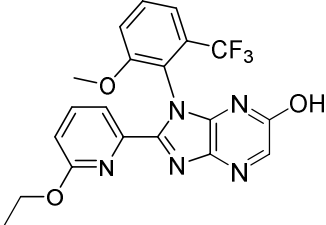
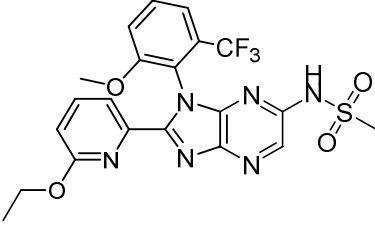
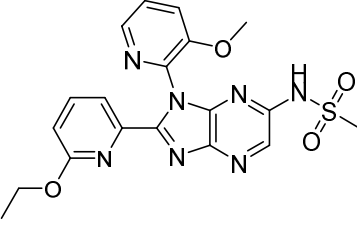
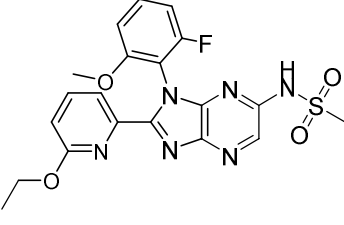
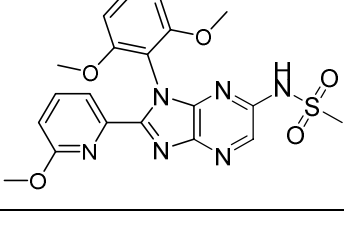
11		N,N-dibenzyl-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-amine
12		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-N,N-dimethyl-1H-imidazo[4,5-b]pyrazin-6-amine
13		N-benzyl-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-amine
14		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-2-phenylacetamide
15		5-chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazine
16		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-amine
17		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-phenylacetamide

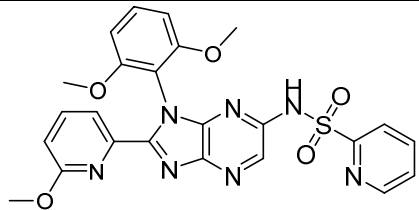
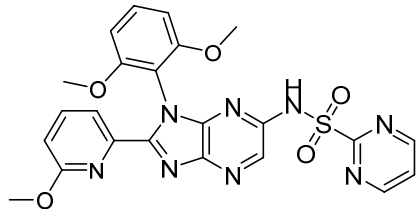
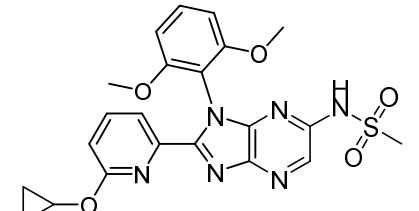
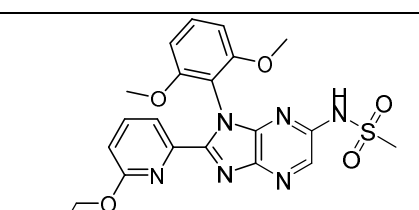
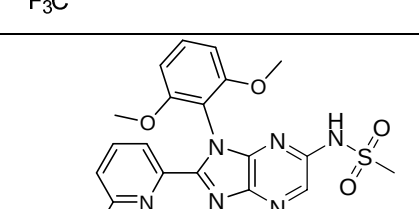
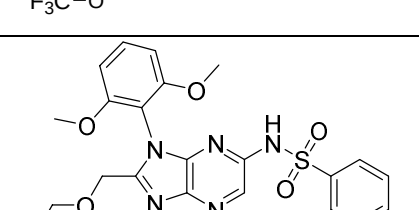
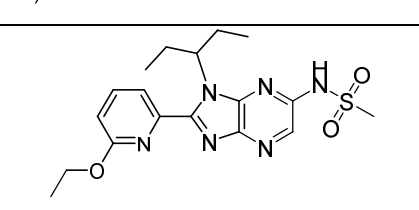
18		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazine
19		N-(5-(2,6-dimethoxyphenyl)-6-(6-ethoxypyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)methanesulfonamide
20		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyridin-6-yl)methanesulfonamide
21		N-(5-(2,6-dimethoxyphenyl)-6-(6-ethoxypyridin-2-yl)-5H-imidazo[4,5-c]pyridazin-3-yl)methanesulfonamide
22		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)cyclopropanesulfonamide
23		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-2-sulfonamide
24		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-3-sulfonamide

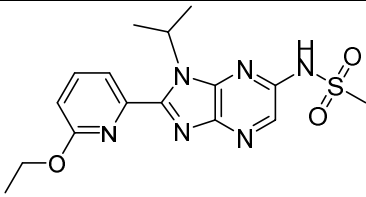
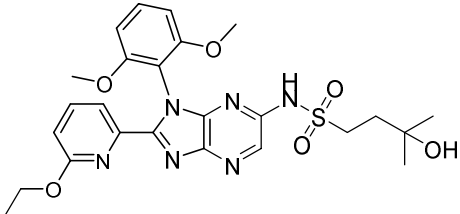
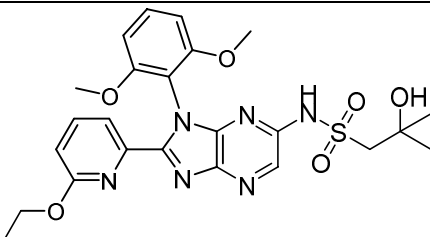
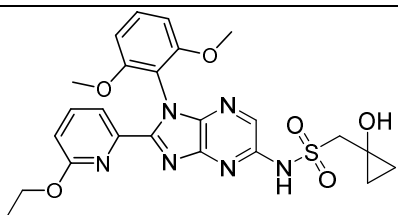
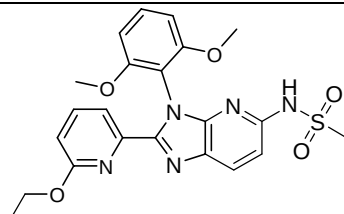
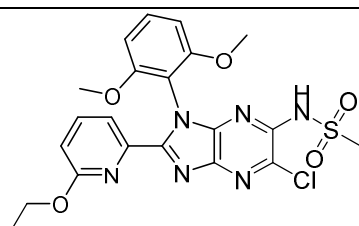
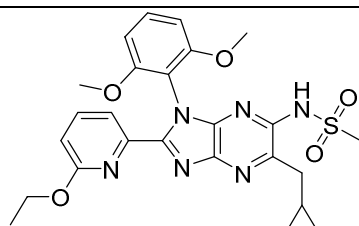
25		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-4-sulfonamide
26		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyridin-3-yl)methanesulfonamide
27		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyridin-2-yl)methanesulfonamide
28		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyrimidin-2-yl)methanesulfonamide
29		2-cyclopropyl-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)ethanesulfonamide
30		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)oxetane-3-sulfonamide
31		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)cyclobutanesulfonamide

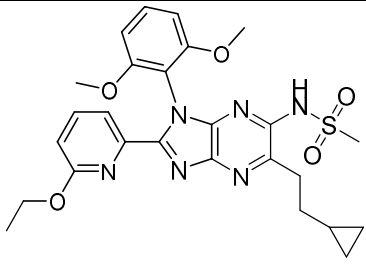
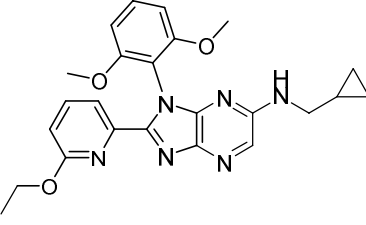
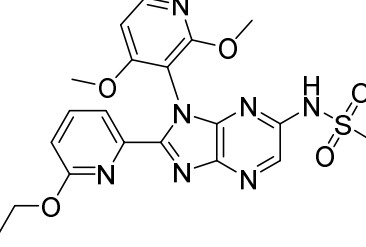
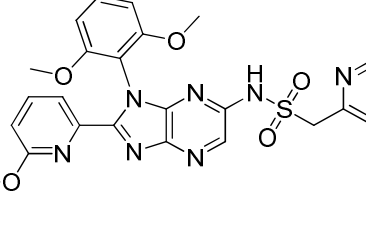
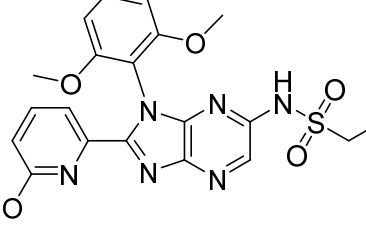
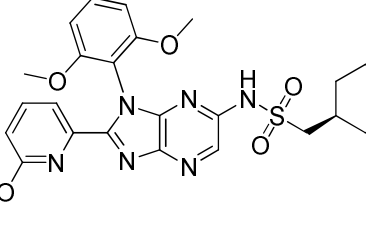
32		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-N-methylmethanesulfonamide
33		cis-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-3-hydroxycyclobutane-1-sulfonamide
34		trans-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-3-hydroxycyclobutane-1-sulfonamide
35		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyrimidin-5-yl)methanesulfonamide
36		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)tetrahydro-2H-pyran-4-sulfonamide
37		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)morpholine-4-sulfonamide
38		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(piperidin-4-yl)methanesulfonamide

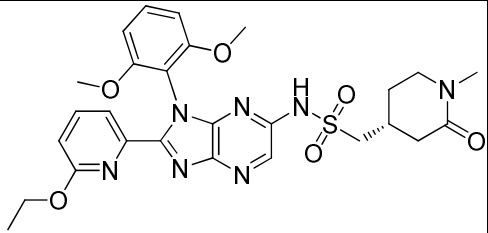
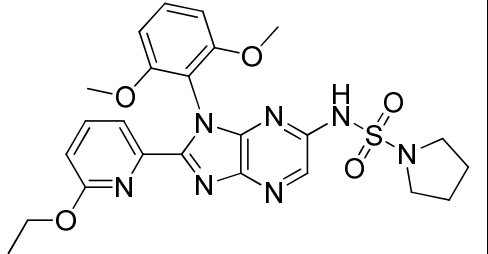
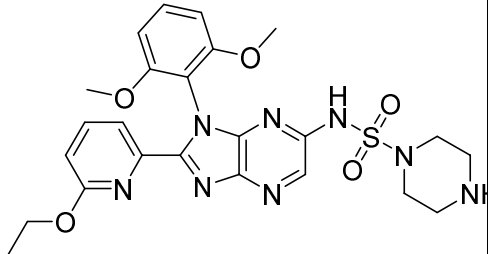
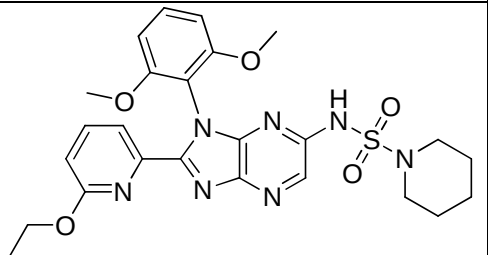
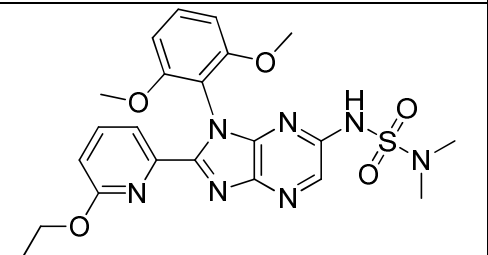
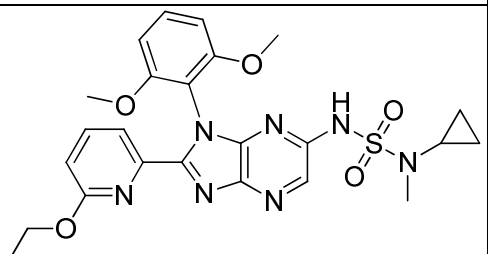
39		trans-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-hydroxycyclohexane-1-sulfonamide
40		cis-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-hydroxycyclohexane-1-sulfonamide
41		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyrimidine-2-sulfonamide
42		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-hydroxypiperidine-1-sulfonamide
43		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)methanesulfonamide
44		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)methanesulfonamide
45		1-cyclopropyl-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)methanesulfonamide

46		1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-N-(4-methoxybenzyl)-1H-imidazo[4,5-b]pyrazin-5-amine
47		2-(6-ethoxypyridin-2-yl)-1-(2-methoxy-6-(trifluoromethyl)phenyl)-1H-imidazo[4,5-b]pyrazin-6-ol
48		N-(2-(6-ethoxypyridin-2-yl)-1-(2-methoxy-6-(trifluoromethyl)phenyl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
49		N-(2-(6-ethoxypyridin-2-yl)-1-(3-methoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
50		N-(benzylsulfonyl)-4-(2-fluoro-6-methoxyphenyl)-5-(6-methoxypyridin-2-yl)-4H-1,2,4-triazole-3-carboxamide
51		N-(1-(2,6-dimethoxyphenyl)-2-(6-methoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide

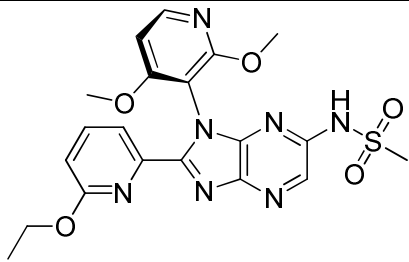
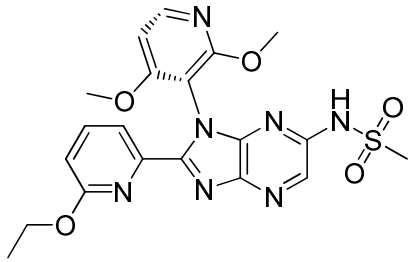
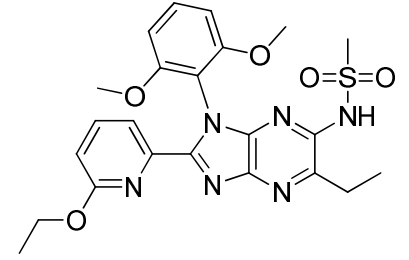
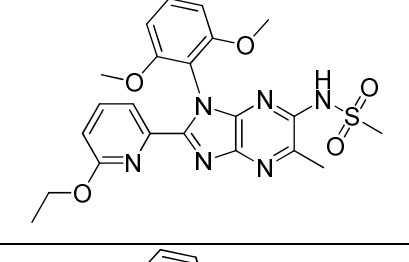
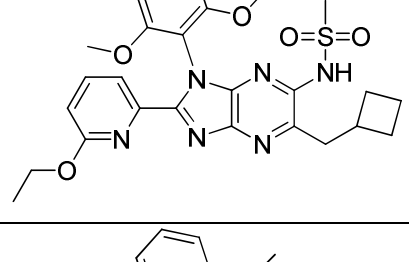
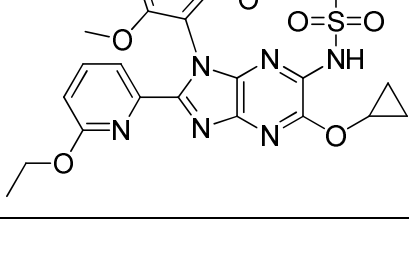
52		N-(1-(2,6-dimethoxyphenyl)-2-(6-methoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-2-sulfonamide
53		N-(1-(2,6-dimethoxyphenyl)-2-(6-methoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyrimidine-2-sulfonamide
54		N-(2-(6-cyclopropoxypyridin-2-yl)-1-(2,6-dimethoxyphenyl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
55		N-(1-(2,6-dimethoxyphenyl)-2-(6-(trifluoroethoxy)pyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
56		N-(1-(2,6-dimethoxyphenyl)-2-(6-(trifluoromethoxy)pyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
57		N-(1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-1H-imidazo[4,5-b]pyrazin-6-yl)benzenesulfonamide
58		N-(2-(6-ethoxypyridin-2-yl)-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide

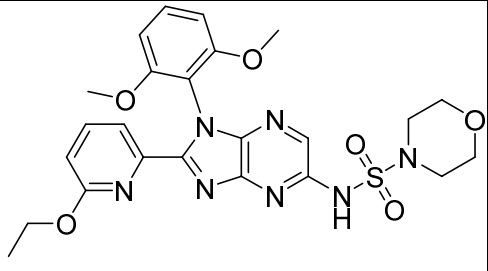
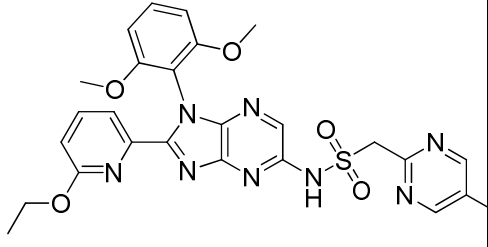
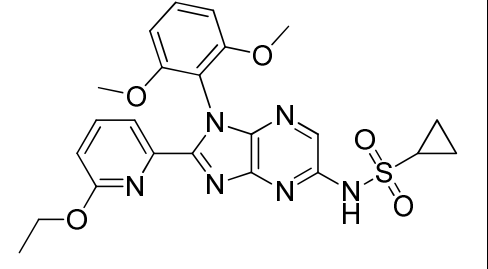
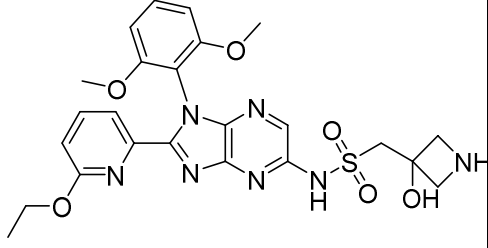
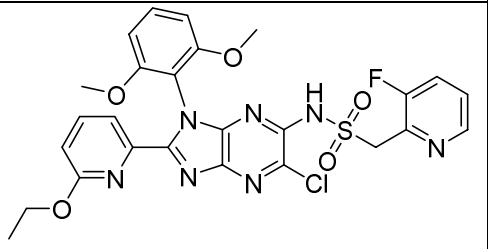
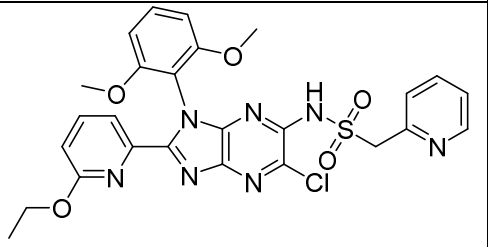
59		N-(2-(6-ethoxypyridin-2-yl)-1-isopropyl-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
60		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-3-hydroxy-3-methylbutane-1-sulfonamide
61		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(1-hydroxycyclopropyl)methanesulfonamide
62		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)-1-(1-hydroxycyclopropyl)methanesulfonamide
63		N-(3-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-5-yl)methanesulfonamide
64		N-(5-chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
65		N-(5-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide

66		N-(5-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
67		N-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-amine
68		N-(1-(2,4-dimethoxypyridin-3-yl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
69		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyrazin-2-yl)methanesulfonamide
70		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-2-hydroxy-2-methylpropane-1-sulfonamide
71		(S)-N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(1-methyl-2-oxopiperidin-4-yl)methanesulfonamide

72		(R)-N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(1-methyl-2-oxopiperidin-4-yl)methanesulfonamide
73		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyrrolidine-1-sulfonamide
74		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)piperazine-1-sulfonamide
75		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)piperidine-1-sulfonamide
76		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-N', N'-dimethylsulfamide
77		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-N'-methyl-N'-cyclopropylsulfamide

78		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-fluoropyridin-2-yl)methanesulfonamide
79		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-fluoropyrimidin-2-yl)methanesulfonamide
80		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-methylpyrimidin-2-yl)methanesulfonamide
81		trans-N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-((1r,3r)-3-hydroxy-3-methylcyclobutyl)methanesulfonamide
82		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-but-2-yn-1-sulfonamide
83		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-methylpyridin-2-yl)methanesulfonamide

84		N-(1-(2,4-Dimethoxypyridin-3-yl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamid
85		N-(1-(2,4-Dimethoxypyridin-3-yl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide]
86		N-(1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-ethyl-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
87		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-methyl-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
88		N-(5-(Cyclobutylmethyl)-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
89		N-(5-Cyclopropoxy-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide

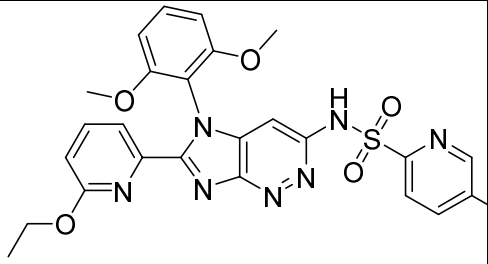
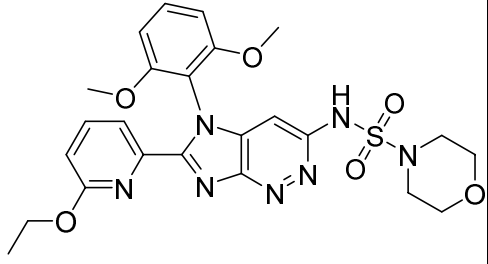
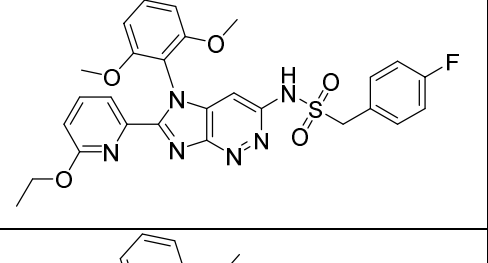
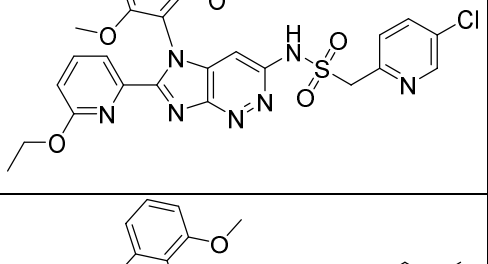
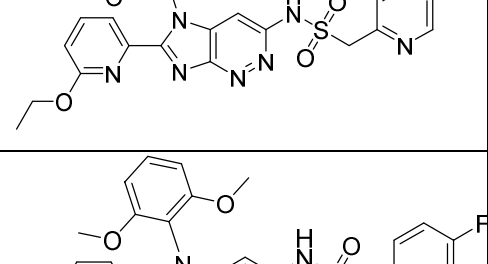
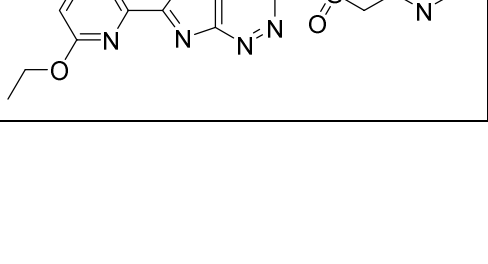
90		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)morpholine-4-sulfonamide
91		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)-1-(5-methylpyrimidin-2-yl)methanesulfonamide
92		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)cyclopropanesulfonamide
93		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)-1-(3-hydroxyazetidin-3-yl)methanesulfonamide
94		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(3-fluoropyridin-2-yl)methanesulfonamide
95		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyridin-2-yl)methanesulfonamide

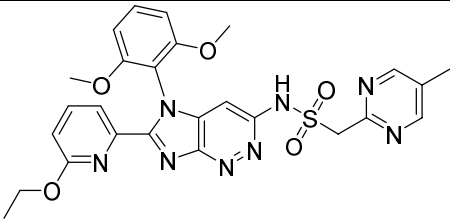
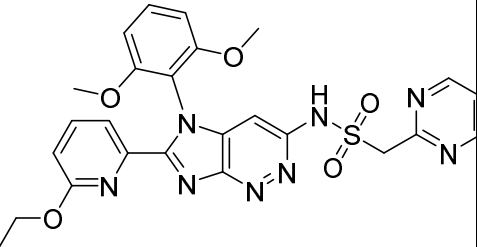
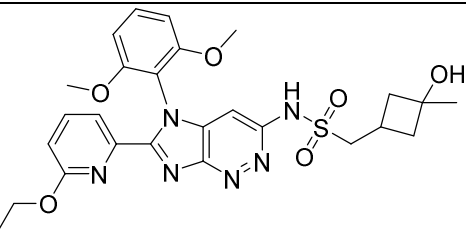
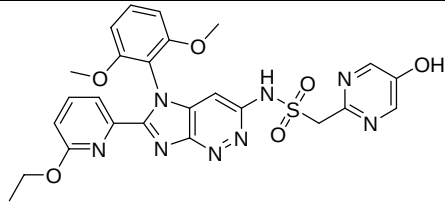
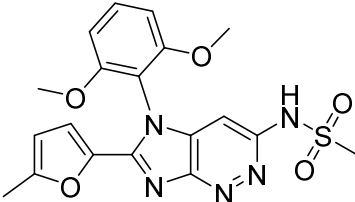
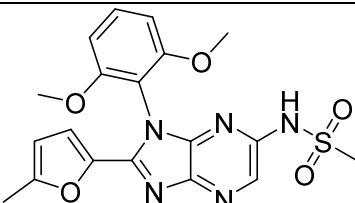
96		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-fluoropyridin-2-yl)methanesulfonamide
97		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)cyclopropanesulfonamide
98		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)morpholine-4-sulfonamide
99		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-5-fluoropyridine-2-sulfonamide
100		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(2-fluoro-4-methylphenyl)methanesulfonamide
101		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-5-methylpyridine-2-sulfonamide

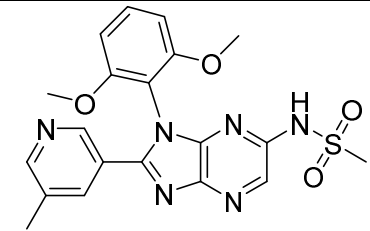
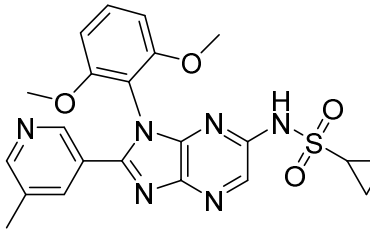
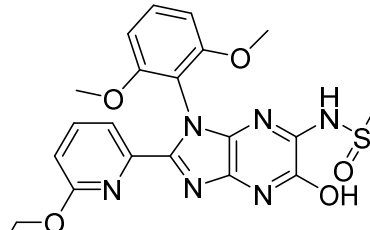
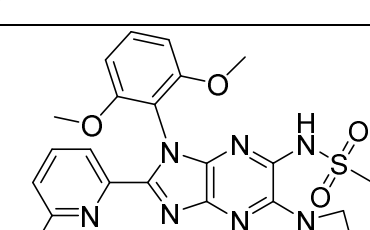
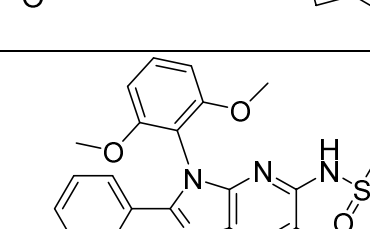
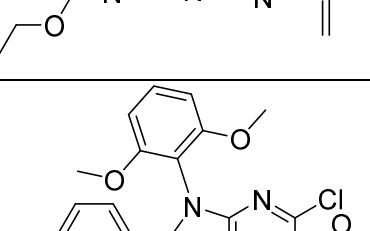
102		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-2-sulfonamide
103		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-(fluoromethyl)benzenesulfonamide
104		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)pyridine-3-sulfonamide
105		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-fluoropyrimidin-2-yl)methanesulfonamide
106		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-(difluoromethyl)benzenesulfonamide
107		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(3-fluoro-4-methylphenyl)methanesulfonamide

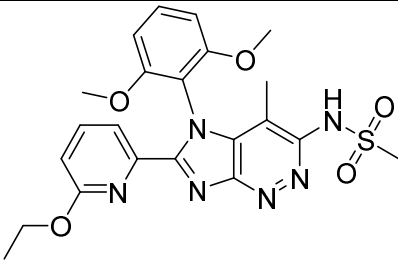
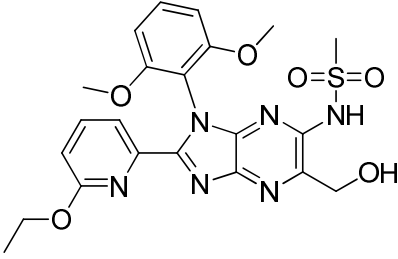
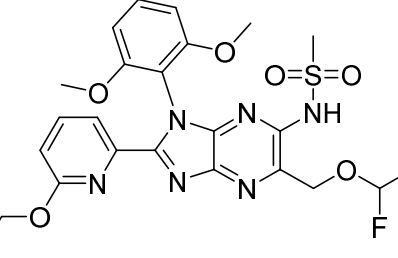
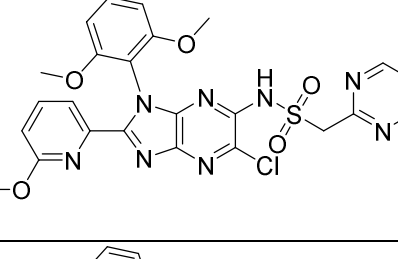
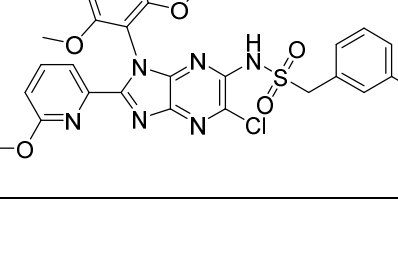
108		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(4-fluorophenyl)methanesulfonamide
109		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(pyrimidin-2-yl)methanesulfonamide
110		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-but-2-yn-1-ylmethanesulfonamide
111		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(tetrahydro-2H-pyran-4-yl)methanesulfonamide
112		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-N'-methyl-N'-cyclopropylmethanesulfonamide
113		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(1-hydroxycyclopropyl)methanesulfonamide

114		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-methylpyridin-2-yl)methanesulfonamide
115		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-((1r, 3r)-3-hydroxy-3-methylcyclobutyl)methanesulfonamide
116		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-4-hydroxypiperidine-1-sulfonamide
117		N-(5-Chloro-1-(3,5-dimethoxypyridin-4-yl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
118		N-(5-Chloro-1-(3,5-dimethoxypyridin-4-yl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)cyclopropanesulfonamide
119		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)cyclopropanesulfonamide

120		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-5-fluoropyridine-2-sulfonamide
121		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)morpholine-4-sulfonamide
122		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-1-(4-fluorophenyl)methanesulfonamide
123		1-(5-Chloropyridin-2-yl)-N-(7-(2,6-dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)methanesulfonamide
124		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-1-(5-methylpyridin-2-yl)methanesulfonamide
125		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-1-(5-fluoropyridin-2-yl)methanesulfonamide

126		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-1-(5-methylpyrimidin-2-yl)methanesulfonamide
127		N-(5-(2,6-Dimethoxyphenyl)-6-(6-ethoxypyridin-2-yl)-5H-imidazo[4,5-c]pyridazin-3-yl)-1-(pyrimidin-2-yl)methanesulfonamide
128		N-(5-(2,6-Dimethoxyphenyl)-6-(6-ethoxypyridin-2-yl)-5H-imidazo[4,5-c]pyridazin-3-yl)-1-(3-hydroxy-3-methylcyclobutyl)methanesulfonamide
129		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-7H-imidazo[4,5-c]pyridazinyl)-1-(5-hydroxypyrimidin-2-yl)methanesulfonamide
130		N-(7-(2,6-Dimethoxyphenyl)-8-(5-methylfuran-2-yl)-7H-imidazo[4,5-c]pyridazinyl)methanesulfonamide
131		N-(1-(2,6-dimethoxyphenyl)-2-(5-methylfuran-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide

132		N-(1-(2,6-dimethoxyphenyl)-2-(5-methylpyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
133		N-(1-(2,6-dimethoxyphenyl)-2-(5-methylpyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)cyclopropanesulfonamide
135		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-hydroxy-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
136		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-(3-hydroxyazetidin-1-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
137		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-vinyl-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
138		N-(6-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)methanesulfonamide

139		N-(7-(2,6-Dimethoxyphenyl)-8-(6-ethoxypyridin-2-yl)-6-methyl-7H-imidazo[4,5-c]pyridazinyl)methanesulfonamide
140		N-(1-(2,6-Dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-5-(hydroxymethyl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
141		N-(5-((Difluoromethoxy)methyl)-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)methanesulfonamide
142		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(5-methylpyrimidin-2-yl)methanesulfonamide
143		N-(5-Chloro-1-(2,6-dimethoxyphenyl)-2-(6-ethoxypyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-6-yl)-1-(3-fluorophenyl)methanesulfonamide

and a pharmaceutically acceptable salt thereof.

60. A pharmaceutical composition comprising a compound or salt as claimed in any one of the preceding claims and one or more pharmaceutically acceptable excipients.

61. A method for modulating APJ receptor activity, the method comprising contacting the APJ receptor with a compound as claimed in any one of claims 1-59.
62. Use of a compound as claimed in any one of claims 1-59 in the manufacture of a medicament for treating a disease, disorder, or condition, in which repressed or impaired APJ receptor signaling, or downregulation of endogenous apelin contributes to the pathology and/or symptoms and/or progression of the disease, disorder, or condition.
63. The use according to claim 62, wherein the disease, disorder, or condition is pulmonary arterial hypertension (“PAH”).
64. The use according to claim 63, wherein the PAH is idiopathic.
65. The use according to claim 63, wherein the PAH is heritable PAH, toxin or drug-induced PAH; or a PAH associated with one or more of the following: congenital heart disease, connective tissue disorders (e.g., scleroderma, systemic lupus erythematosus, systemic sclerosis, Hashimoto's thyroiditis, Sjogren's Syndrome, and the antiphospholipid antibody syndrome), portal hypertension, BMPR2 mutations, Schistosomiasis, and HIV infection.
66. The use according to claim 62, wherein the disease, disorder, or condition is fibrosis.
67. The use according to claims 62 and 66, wherein the the disease, disorder, or condition is idiopathic pulmonary fibrosis (IPF).
68. The use according to claim 62, wherein the disease, disorder, or condition is a connective tissue disorder.