(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2017 (21.12.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/218617 A1

(51) International Patent Classification:
C07D 213/71 (2006.01) *C07D 471/04* (2006.01)
C07D 213/74 (2006.01) *A61K 31/444* (2006.01)
C07D 213/89 (2006.01) *A61P 9/10* (2006.01)
C07D 401/12 (2006.01)

(21) International Application Number:
PCT/US2017/037370

(22) International Filing Date:
14 June 2017 (14.06.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/349,719 14 June 2016 (14.06.2016) US

(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(72) Inventors: **JIANG, Ji**; c/o Bristol-Myers Squibb Company, 350 Carter Road, Hopewell, New Jersey 08534 (US). **FINLAY, Heather**; c/o Bristol-Myers Squibb Company, 350 Carter Road, Hopewell, New Jersey 08534 (US). **KIM, Soong-Hoon**; c/o Bristol-Myers Squibb Company, 350 Carter Road, Hopewell, New Jersey 08534 (US). **MENG, Wei**; c/o Bristol-Myers Squibb Company, 350 Carter Road, Hopewell, New Jersey 08534 (US). **TORA, George O.**; c/o Bristol-Myers Squibb Company, 350 Carter Road, Hopewell, New Jersey 08534 (US).

(74) Agent: **LIU, Hong** et al.; Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

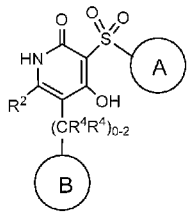
Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

WO 2017/218617 A1

(54) Title: 4-HYDROXY-3-SULFONYLPYRIDIN-2(1H)-ONES AS APJ RECEPTOR AGONISTS

(57) Abstract: The present invention provides compounds of Formula (I) wherein all variables are as defined in the specification, and compositions comprising any of such novel compounds. These compounds are APJ agonists which may be used as medicaments.



(I)

4-HYDROXY-3-SULFONYLPYRIDIN-2(1H)-ONES AS APJ RECEPTOR AGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. §119(e) to U.S. provisional patent application No. 62/349,719, filed June 14, 2016, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention provides novel sulfonylpyridine compounds, and their analogues thereof, which are APJ agonists, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of heart failure, atherosclerosis, ischemic heart disease and related conditions.

BACKGROUND OF THE INVENTION

Heart failure (HF) and related complications constitute major health burden in developed countries with an estimated prevalence of 5,700,000 in the United States alone (Roger, V.L. et al., *Circulation*, 125(1):e2-e220 (2012)). Despite considerable advances in recent two decades, the prognosis remains very poor, with survival rates of only ~50% within 5-years of diagnosis (Roger, V.L. et al., *JAMA*, 292(3):344-350 (2004)). In addition to poor survival, the impaired quality of life and recurrent hospitalizations constitute clear unmet medical need for development of novel treatment options.

HF is a clinical syndrome characterized by the inability of the heart to deliver sufficient supply of blood and oxygen to meet the metabolic demands of organs in the body. Main symptoms associated with HF include shortness of breath due to pulmonary edema, fatigue, reduced tolerance to exercise and lower extremity edemas. The etiology of HF is highly complex with multiple associated risk factors and potential causes.

Among the leading causes of HF are coronary artery disease and cardiac ischemia, acute myocardial infarction, intrinsic cardiomyopathies and chronic uncontrolled hypertension. HF can develop either acutely (functional impairment post myocardial infarction) or as a chronic condition, characterized by long-term maladaptive cardiac tissue remodeling, hypertrophy and cardiac dysfunction (for example due to uncontrolled long-term hypertension). According to the diagnostic criteria and type of ventricular

dysfunction, HF is classified to two major groups, HF with "reduced ejection fraction" (HFrEF) or HF with "preserved ejection fraction" (HFpEF). Both types are associated with similar signs and symptoms, but differ in the type of ventricular functional impairment (Borlaug, B.A. et al., *Eur. Heart J.*, 32(6):670-679 (2011)).

APJ receptor (APLNR) and its endogenous peptidic ligand apelin have been implicated as important modulators of cardiovascular function and candidates for therapeutic intervention in HF (for review see Japp, A.G. et al., *Biochem. Pharmacol.*, 75(10):1882-1892 (2008)).

Accumulated evidence from preclinical disease models and human heart failure patients have implicated apelin and APJ agonism as beneficial in the setting of HF. Mice lacking Apelin or APJ gene have impaired myocyte contractility (Charo, D.N. et al., *Am. J. Physiol. Heart Circ. Physiol.*, 297(5):H1904-H1913 (2009)). Apelin knockout (KO) mice develop progressive cardiac dysfunction with aging and are more susceptible to HF in the model of trans-aortic constriction (TAC) (Kuba, K. et al., *Circ. Res.*, 101(4):e32-42 (2007)). The functional impairment in chronic HF is a result of prolonged demand on the heart and is associated with maladaptive cardiac remodeling, manifested by the cardiac hypertrophy, increased inflammation and interstitial fibrosis which eventually lead to decrease in cardiac performance.

Acute administration of apelin increases cardiac output in rodents under normal conditions and also in models of heart failure (Berry, M.F., *Circulation*, 110(11 Suppl. 1):II187-II193 (2004)). Increased cardiac output is a result of direct augmentation of cardiac contractility and reduced peripheral vascular resistance in the arterial and venous beds (Ashley, E.A., *Cardiovasc. Res.*, 65(1):73-82 (2005)). Reduction in the vascular resistance leads to lower pre-load and after-load on the heart and thus lesser work load (Cheng, X. et al., *Eur. J. Pharmacol.*, 470(3):171-175 (2003)). Similar to rodent studies, acute infusion of apelin to healthy human subjects and patients with heart failure produces similar hemodynamic responses with increased cardiac output and increased vasodilatory response in peripheral and coronary arteries (Japp, A.G. et al., *Circulation*, 121(16):1818-1827 (2010)).

The mechanisms underlying inotropic action of apelin are not well understood, but appear to be distinct from clinically used β_1-adrenergic agonists (dobutamine) due to lack of increase in heart rate. The vasodilatory action of apelin is primarily mediated via

endothelial nitric oxide synthase pathways (Tatemoto, K., *Regul. Pept.*, 99(2-3):87-92 (2001)). Apelin is induced under hypoxic conditions, promotes angiogenesis and has been shown to limit the infarct size in ischemia-reperfusion models (Simpkin, J.C., *Basic Res. Cardiol.*, 102(6):518-528 (2007)).

In addition to aforementioned studies evaluating acute administration of apelin, several studies have clearly demonstrated beneficial effects of prolonged administration of apelin in a number of chronic rodent models of HF, including the angiotensin II model, TAC model and rat Dahl salt-sensitive model (Siddiquee, K. et al., *J. Hypertens.*, 29(4):724-731 (2011); Scimia, M.C. et al., *Nature*, 488(7411):394-398 (2012); Koguchi, W. et al., *Circ. J.*, 76(1):137-144 (2012)). In these studies, prolonged apelin infusion reduced cardiac hypertrophy and cardiac fibrosis, and was associated with improvement in cardiac performance.

Genetic evidence is also emerging that polymorphisms in the APJ gene are associated with slower progression of HF (Sarzani, R. et al., *J. Card. Fail.*, 13(7):521-529 (2007)). Importantly, while expression of APJ and apelin can be reduced or vary considerably with HF progression, the cardiovascular hemodynamic effects of apelin are sustained in patients with developed HF and receiving standard of care therapy (Japp, A.G. et al., *Circulation*, 121(16):1818-1827 (2010)).

In summary, there is a significant amount of evidence to indicate that APJ receptor agonism plays a cardioprotective role in HF and would be of potential benefit to HF patients. Apelin's very short half life in circulation limits its therapeutic utility, and consequently, there is a need for APJ receptor agonists with improved pharmacokinetic and signaling profile while maintaining or enhancing the beneficial effects of endogenous APJ agonist apelin.

SUMMARY OF THE INVENTION

The present invention provides sulfonylpyridine compounds, and their analogues thereof, which are useful as APJ agonists, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ, such as heart failure, coronary artery disease, cardiomyopathy, diabetes and related conditions including but not limited to acute coronary syndrome, myocardial ischemia, hypertension, pulmonary hypertension, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, angina, renal disease, metabolic syndrome and insulin resistance.

The compounds of the invention may be used in therapy.

The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ.

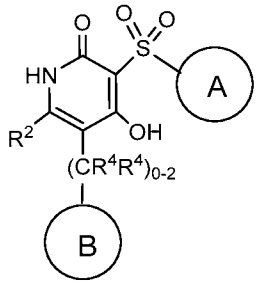
The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

In one aspect, the present disclosure provides, *inter alia*, compounds of Formula (I):



(I)

or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

ring A is independently selected from -$(CH_2)_{0-1}$-5- or 6-membered aryl and heterocyclyl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^{3a}, O, and S, each substituted with 1-3 R^3 and 1-2 R^5 ; provided R^3 and R^5 are not both H;

ring B is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, aryl, bicyclic carbocyclyl, 6-membered heteroaryl, and bicyclic heterocyclyl, each substituted with 1-3 R^1;

R^1 is independently selected from H, F, Cl, Br, NO_2, -$(CH_2)_nOR^b$, $(CH_2)_nS(O)_pR_c$, -$(CH_2)_nC(=O)R^b$, -$(CH_2)_nNR^aR^a$, -$(CH_2)_nCN$, -$(CH_2)_nC(=O)NR^aR^a$, -$(CH_2)_nNR^aC(=O)R^b$, -$(CH_2)_nNR^aC(=O)NR^aR^a$, -$(CH_2)_nNR^aC(=O)OR^b$, -$(CH_2)_nOC(=O)NR^aR^a$, -$(CH_2)_nC(=O)OR^b$, -$(CH_2)_nS(O)_pNR^aR^a$, -$(CH_2)_nNR^aS(O)_pNR^aR^a$, -$(CH_2)_nNR^aS(O)_pR^c$, C_{1-4} alkyl substituted with 0-3 R^e, -$(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl substituted with 0-3 R^e, aryl substituted with 0-3 R^e, heterocyclyl substituted with 0-3 R^e, and C_{3-6} cycloalkyl substituted with 0-3 R^e; provided when R^2 is C_{1-5} alkyl, the carbon atom except the one attached to the pyridine ring may be replaced by O, N, and S;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, -$(CH_2)_nOR^b$, -$(CH_2)_nNR^aR^a$, -$(CH_2)_nCN$, -$(CH_2)_nC(=O)R^b$, -$(CH_2)_nC(=O)OR^b$, -$(CH_2)_nC(=O)NR^aR^a$, -$(CH_2)_nNHC(=O)R^b$, -$(CH_2)_nNHC(=O)NR^aR^a$, -$(CH_2)_nNHC(=O)OR^b$, -$(CH_2)_nNHS(O)_pNR^aR^a$, -$(CH_2)_nNHS(O)_pR^c$ - $(CH_2)_nS(O)_pR_c$, -$(CH_2)_nS(O)_pNR^aR^a$, and -$(CH_2)_nOC(=O)NR^aR^a$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, -$S(O)_pR_c$, -$C(=O)R^b$, -$C(=O)NR^aR^a$, -$C(=O)OR^b$, $S(O)_pNR^aR^a$, R^6, -$S(O)_pR^6$, -$C(=O)R^6$, -$C(=O)NR^aR^6$, -$C(=O)OR^6$, and -$S(O)_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, R^6, -OR^6, -$S(O)_pR^6$, -$C(=O)R^6$, -$C(=O)OR^6$, -NR^aR^6, -$C(=O)NR^aR^6$, -$NR^aC(=O)R^6$, -$NR^aC(=O)OR^6$, -$OC(=O)NR^aR^6$, -$S(O)_pNR^aR^6$, -$NR^aS(O)_pNR^aR^6$, and -$NR^aS(O)_pR^6$;

R^6 is independently selected from -$(CR^7R^7)_n$-aryl, -$(CR^7R^7)_n$-C_{3-6} cycloalkyl, and -$(CR^7R^7)_n$-heteroaryl, each substituted with 1-6 R^8;

R^7 is independently selected from H, C_{1-4} alkyl, and $(CH_2)_n$-C_{3-12} carbocyclyl substituted with 0-3 R^e;

R^8 is independently selected from H, F, Cl, Br, -$(CH_2)_n$CN, -$(CH_2)_n$$OR^b$, -$(CH_2)_n$$C(=O)R^b$, -$(CH_2)_n$$C(=O)OR^b$, -$(CH_2)_n$$C(=O)NR^aR^a$, -$(CH_2)_n$$NR^aR^a$, -$(CH_2)_n$$NR^aC(=O)R^b$, -$(CH_2)_n$$NR^aC(=O)OR^b$, -$(CH_2)_n$$NR^aC(=O)NR^aR^a$, -$(CH_2)_n$$OC(=O)NR^aR^a$, -$(CH_2)_n$$S(O)_pR_c$, -$(CH_2)_n$$S(O)_pNR^aR^a$, -$(CH_2)_n$$NR^aS(O)_pNR^aR^a$, -$(CH_2)_n$$NR^aS(O)_pR^c$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

R^c is independently selected from C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6}alkenyl substituted with 0-5 R^e, C_{2-6}alkynyl substituted with 0-5 R^e, C_{3-6}carbocyclyl, and heterocyclyl;

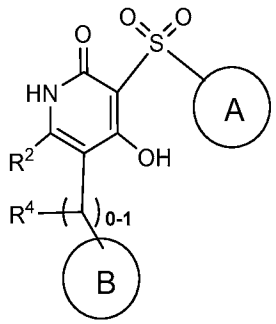
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, -$(CH_2)_n$$OR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and -$(CH_2)_n$$NR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl, or R^f and R^f together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with C_{1-4}alkyl;

n is independently selected from zero, 1, 2, 3, and 4; and

p is independently selected from zero, 1, and 2.

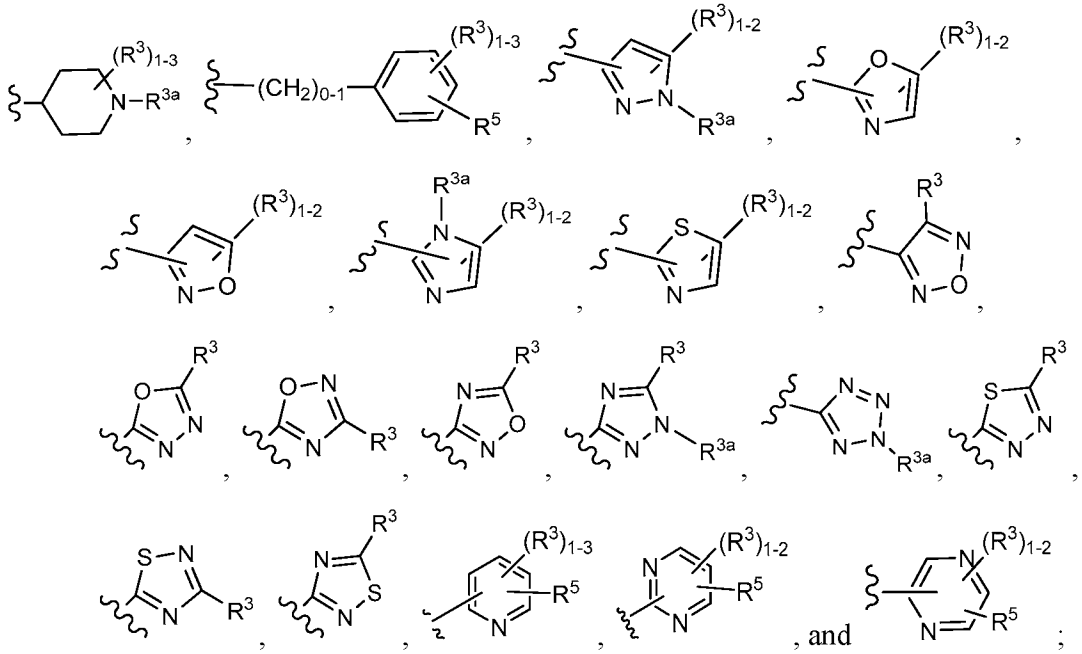
In another aspect, the present invention provides compounds of Formula (II):



(II)

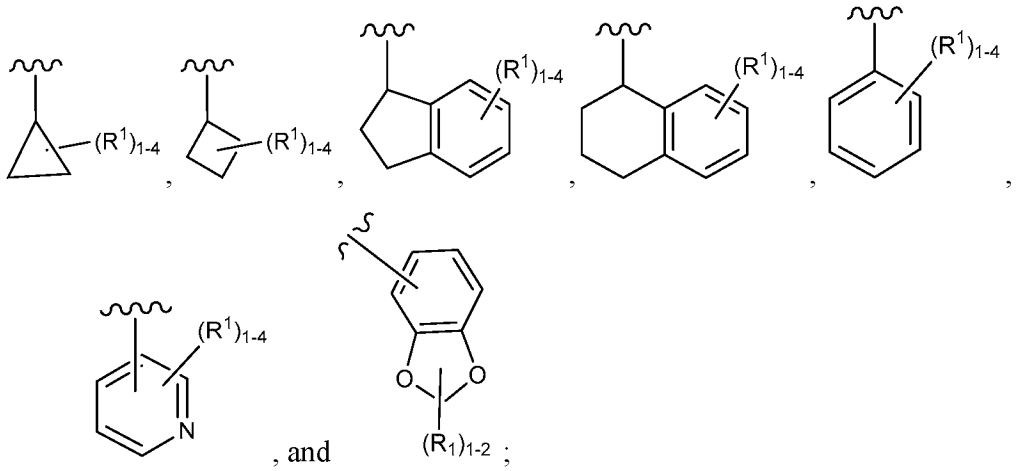
or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

ring A is independently selected from



; and

ring B is independently selected from



, and ;

R^1 is independently selected from H, F, Cl, Br , $-OR^b$, CN, C_{1-4} alkyl substituted with 0-3 R^e and C_{3-6} cycloalkyl substituted with 0-3 R^e;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, heterocyclyl substituted with 0-3 R^e, and C_{3-6} cycloalkyl; provided when R^2 is C_{1-5} alkyl, the carbon atom except the one attached to the pyridine ring may be replaced by O, N, and S;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl; $-OR^b$, $-NR^aR^a$, -CN, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-NHC(=O)R^b$, $-NHC(=O)NR^aR^a$, $-NHC(=O)OR^b$, $-NHS(O)_pR^c$ $-S(O)_pR_c$, $-S(O)_pNR^aR^a$, and $-OC(=O)NR^aR^a$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, R^6, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $-(CH_2)_n$-C_{3-6} cycloalkyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, R^6, $-OR^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, $-OC(=O)NR^aR^6$, $-S(O)_pNR^aR^6$, $-NR^aS(O)_pNR^aR^6$, and $-NR^aS(O)_pR^6$;

R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

R^7 is independently selected from H and C_{1-4} alkyl;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nNR^aR^a$, CN, $-(CH_2)_nC(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

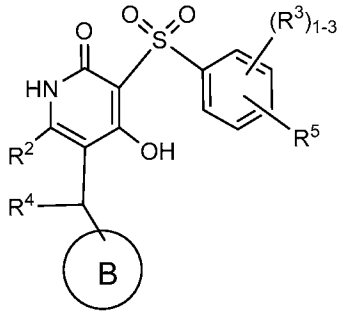
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

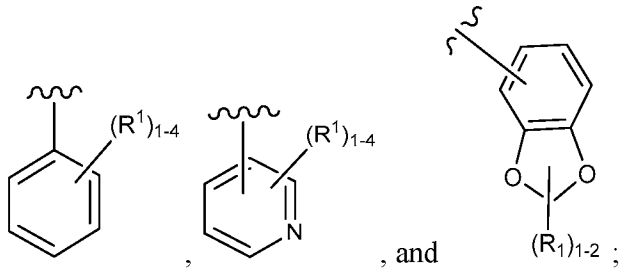
In another aspect, the present invention provides compounds of Formula (III):



(III)

or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

ring B is independently selected from



R^1 is independently selected from H, F, Cl, CN, and OC_{1-4} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, and Br;

R^4 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl, C_{3-6} cycloalkyl substituted with 0-3 R^e, and heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected H and R^6;

R^6 is independently selected from aryl, C_{3-6} cycloalkyl, and heteroaryl, each substituted with 1-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

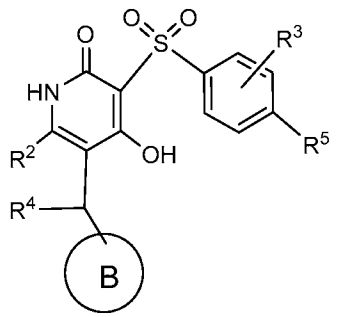
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

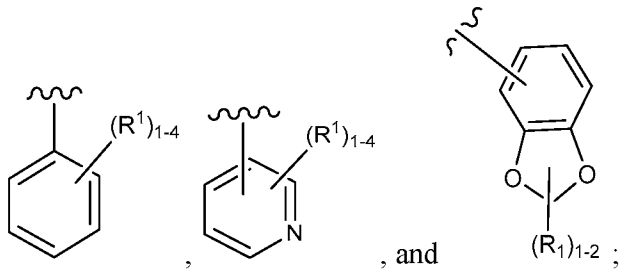
In another aspect, the present invention provides compounds of Formula (IV):



(IV)

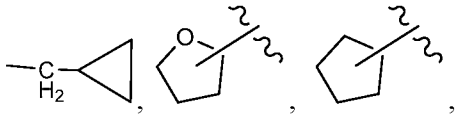
or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

ring B is independently selected from



R^1 is independently selected from H, F, Cl, CN, and OMe;

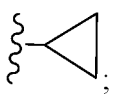
R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,



, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

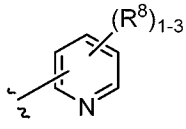
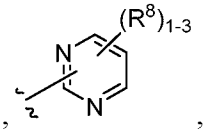
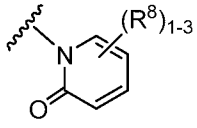
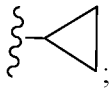
R^3 is independently selected from H, F, Cl, and Br;

R^4 is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH=CH_2$, and



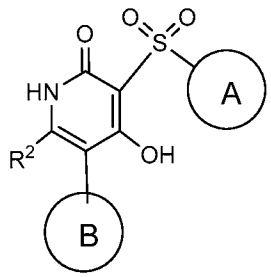
;

R^5 is R^6;

R^6 is independently selected from , , , and ; and

R^8 is independently selected from H, F, Cl, Br, $-OCH_3$, and C_{1-4} alkyl.

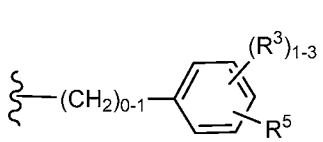
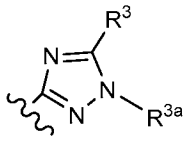
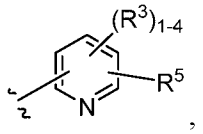
In another aspect, the present invention provides compounds of Formula (V):



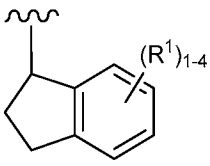
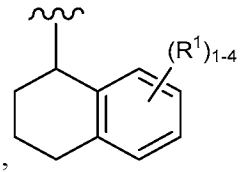
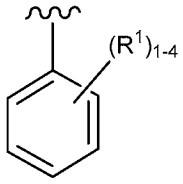
(V)

or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

ring A is independently selected from

, , and ,

ring B is independently selected from

, , and ;

R^1 is independently selected from H, F, Cl, CN, and OC_{1-4} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $-OR^b$, $-NR^aR^a$, -CN, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-NHC(=O)R^b$, and $-NHC(=O)OR^b$;

R^4 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl, C_{3-6} cycloalkyl substituted with 0-3 R^e, and heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, aryl R^6, $-OR^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, $-OC(=O)NR^aR^6$, $-S(O)_pNR^aR^6$, $-NR^aS(O)_pNR^aR^6$, and $-NR^aS(O)_pR^6$;

R^6 is independently selected from aryl, C_{3-6} cycloalkyl, and heteroaryl, each substituted with 1-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

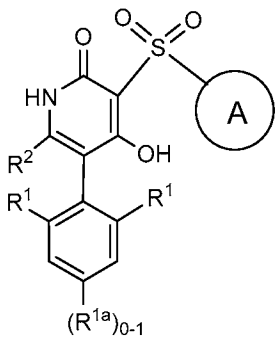
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

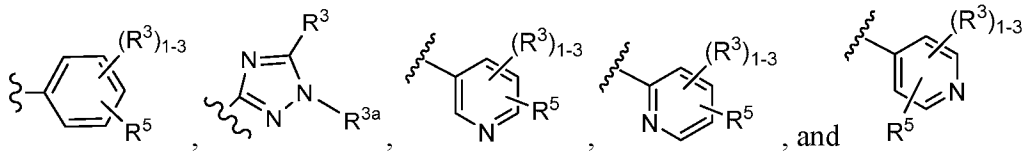
In another aspect, the present invention provides compounds of Formula (VI):



(VI)

or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

ring A is independently selected from



;

R^1 is independently selected from F, Cl, OH, and OC_{1-4} alkyl;

R^{1a} is independently selected from F, Cl, and C_{1-2} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl and $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{1-5} alkyl $-OR^b$, $-NR^aR^a$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-NHC(=O)R^b$, $-NHC(=O)OR^b$, and $-NHC(=O)NHR^a$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, $-R^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $-(CH_2)_n$-C_{3-6} cycloalkyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

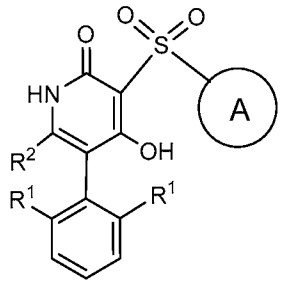
R^5 is independently selected from H, R^6, $-OR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, and $-OC(=O)NR^aR^6$;

R^6 is independently selected from $-(CH_2)_n$-aryl, $-(CH_2)_n$-C_{3-6} cycloalkyl, and $-(CH_2)_n$-heteroaryl, each substituted with 0-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e; and

n is independently selected from zero, 1, 2, and 3.

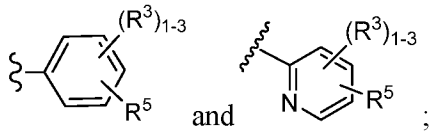
In another aspect, the present invention provides compounds of Formula (VII):



(VII)

or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

ring A is independently selected from



;

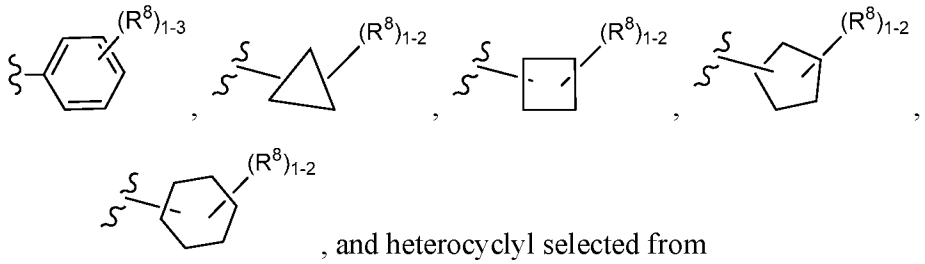
R^1 is $-OC_{1-4}$ alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

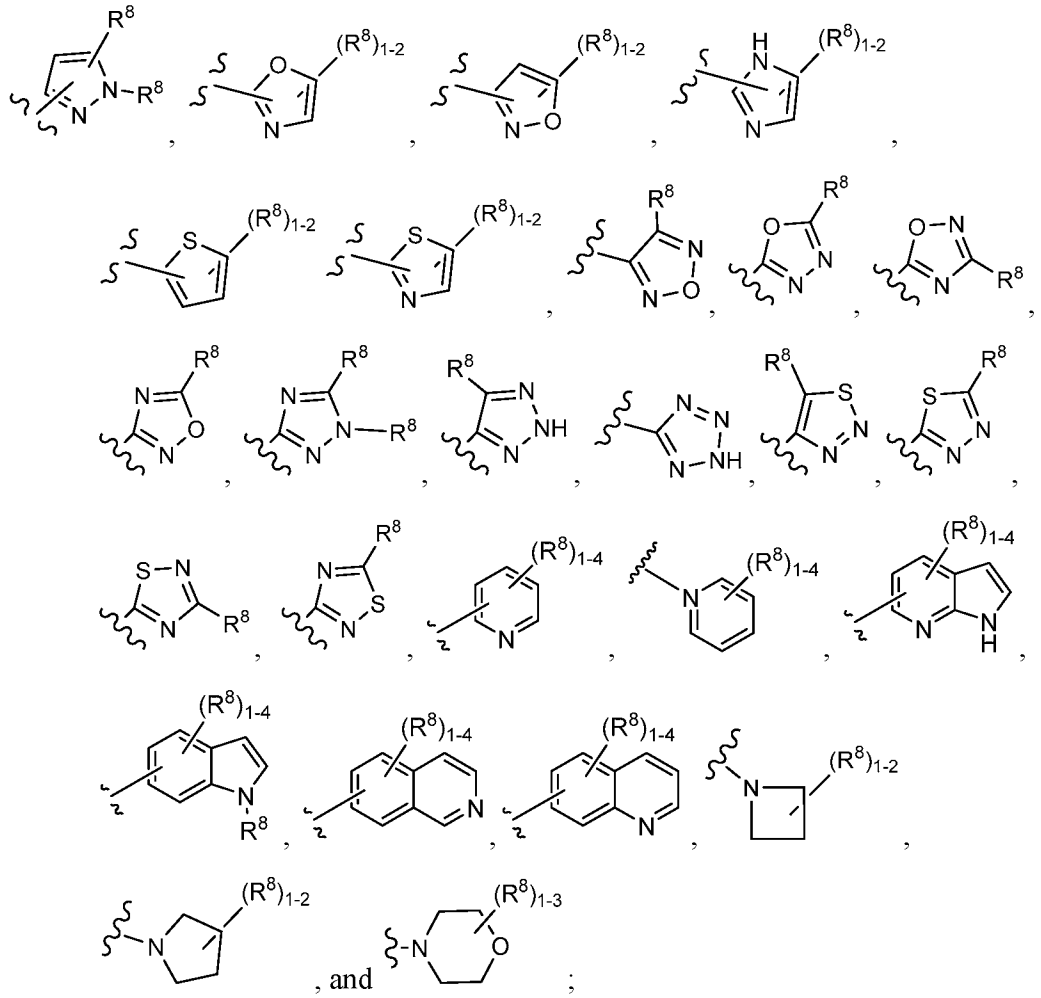
R^3 is independently selected from H, F, Cl, Br, C_{1-4} alkyl, C_{2-4} alkenyl, $-NHR^a$, $-C(=O)OR^a$, $-C(=O)NHR^a$, $-NHC(=O)R^b$, $-NHC(=O)OR^b$, and $-NHC(=O)NHR^a$;

R^5 is independently selected from H, R^6, $-C(=O)R^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, and $-NHC(=O)R^6$

R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from



, and ;

R^8 is independently selected from H, F, Cl, Br, -OR^b, -C(=O)R^b, -C(=O)OR^b, -NR^aR^a, CN, -C(=O)NR^aR^a, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl

substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

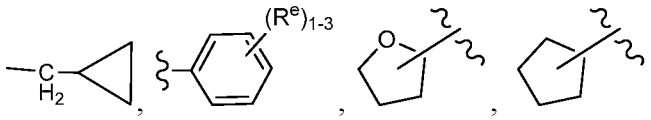
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

In another aspect, the present invention provides compounds of Formula (VII), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

R^1 is $-OC_{1-4}$ alkyl;

R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,

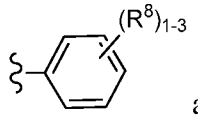


, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

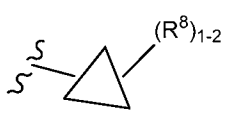
R^3 is independently selected from H, F, Cl, Br, $-C(=CH_2)CH_3$, $-C(=O)OR^b$, $-C(=O)NHR^a$, $-NHC(=O)OR^b$, and $-NHC(=O)NHR^a$;

R^5 is independently selected from R^6, $-C(=O)R^6$, $-NR^aR^6$, $-C(=O)NHR^6$, and $-NHC(O)R^6$;

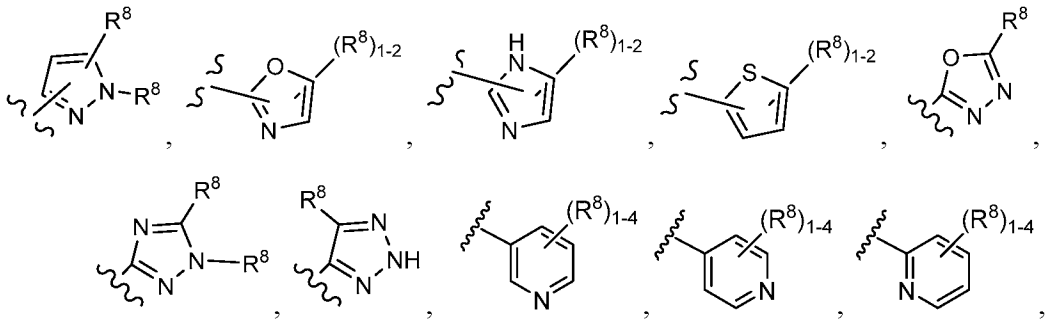
R^6 is independently selected from carbocyclyl selected from

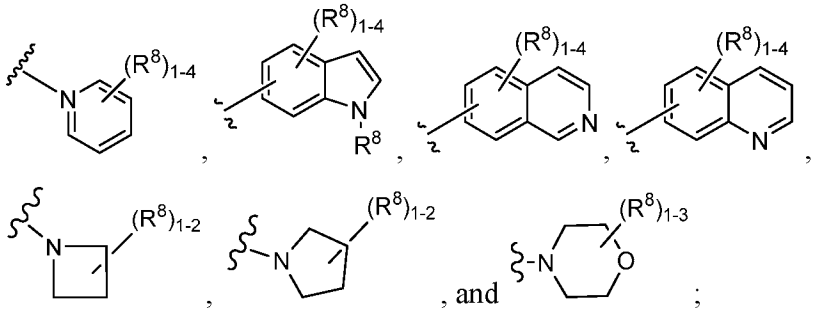


and



, and heterocyclyl selected from





R^8 is independently selected from H, F, Cl, Br, --$(CH_2)_nOR^b$, -C(=O)R^b, -C(=O)OR^b, -$(CH_2)_nNR^aR^a$, CN, -C(=O)NR^aR^a, -NHC(=O)R^b, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

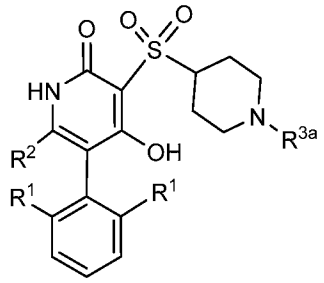
R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

In another aspect, the present invention provides compounds of Formula (VIII):



(VIII)

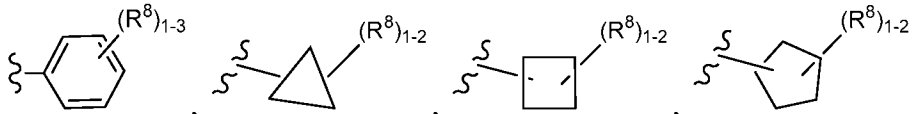
or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

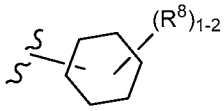
R^1 is -OC_{1-4} alkyl;

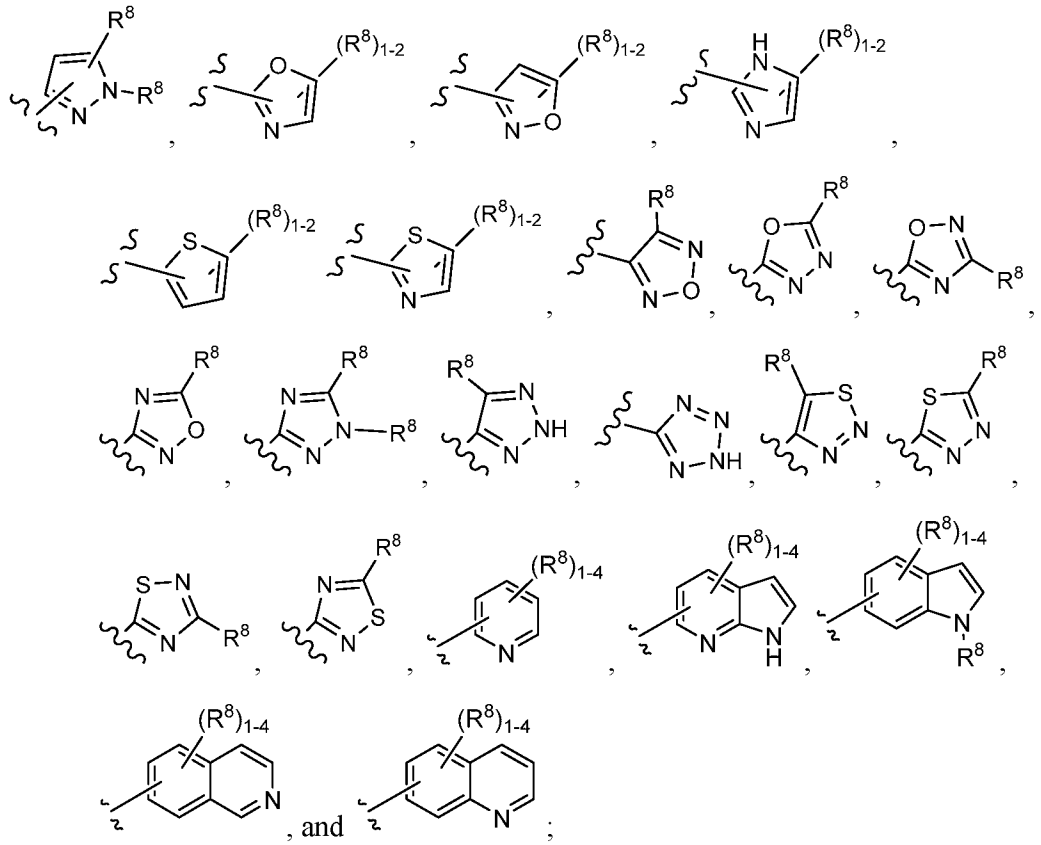
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-S(O)_pR_c$, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, $S(O)_pNR^aR^a$, R^6, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^6 is independently selected from carbocyclyl selected from


, and


, and heterocyclyl selected from


, and

;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6}

carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

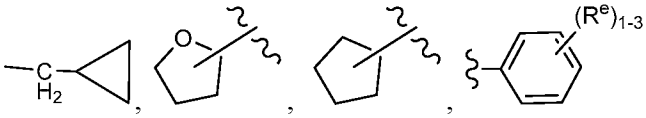
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

In another aspect, the present invention provides compounds of Formula (VIII), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

R^1 is -OC_{1-4} alkyl;

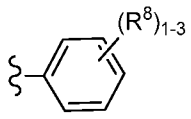
R^2 is independently selected from -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$,



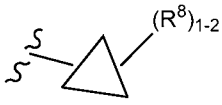
-CH_2OCH_3, -$CH_2OCH_2CH_3$, and -$CH_2OCH(CH_3)_2$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, -C(=O)R^b, -C(=O)OR^b, -$(CH_2)_n$-R^6, and -C(=O)R^6;

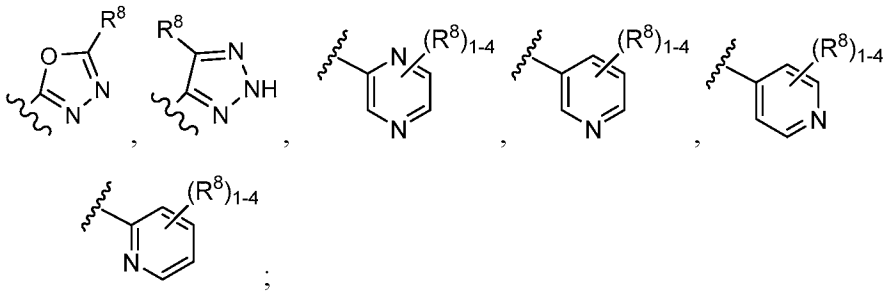
R^6 is independently selected from carbocyclyl selected from



and



, and heterocyclyl selected from



;

R^8 is independently selected from H, F, Cl, Br, --$(CH_2)_nOR^b$, -C(=O)R^b, -C(=O)OR^b, -$(CH_2)_nNR^aR^a$, CN, -C(=O)NR^aR^a, -NHC(=O)R^b, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

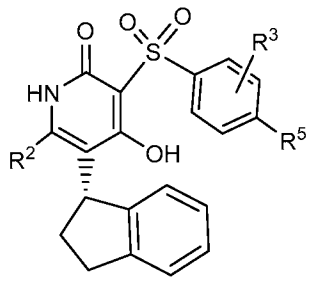
R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H and C_{1-6} alkyl substituted with 0-5 R^e;

R^e is independently selected from OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

In another aspect, the present invention provides compounds of Formula (IX):



(IX)

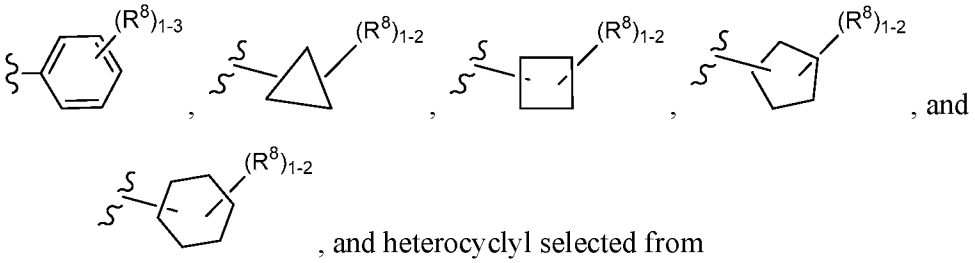
or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, solvate, or prodrugs thereof, wherein

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, heteroaryl substituted with 0-3 R^e, C_{3-6} cycloalkyl, -$(CH_2)_{1-4}OC_{1-5}$alkyl, and -$(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

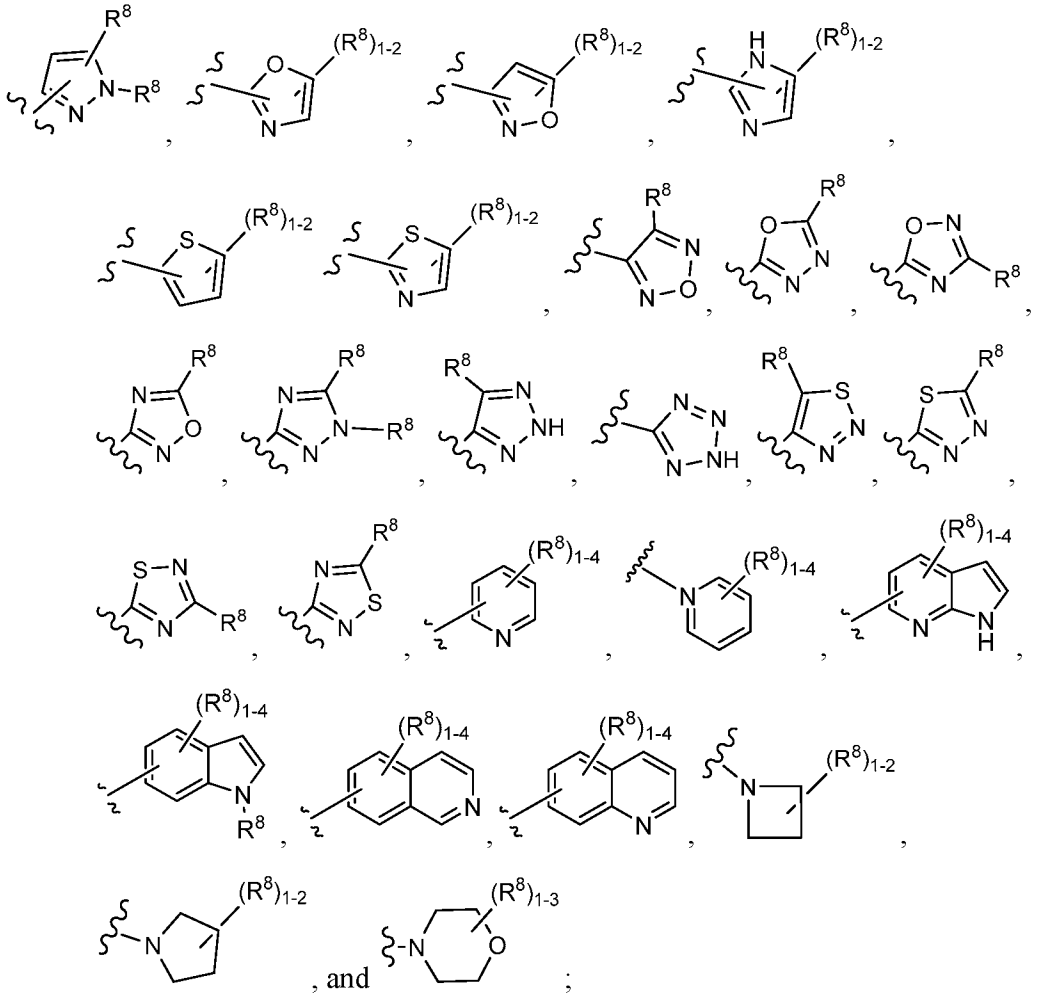
R^3 is independently selected from H, F, Cl, and Br;

R^5 is independently selected from H, R^6, -C(=O)R^6, and -C(=O)N$R^a$$R^6$;

R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from



; and

R^8 is independently selected from H, F, Cl, Br, -OR^b, -C(=O)R^b, -C(=O)OR^b, -N$R^a$$R^a$, CN, -C(=O)N$R^a$$R^a$, -NHC(=O)O$R^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e; $-(CH_2)_n-C_{3-10}$carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

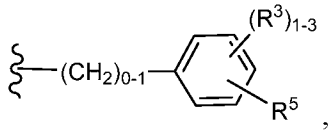
R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

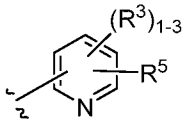
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

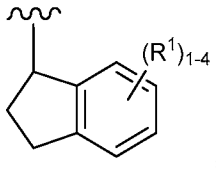
n is independently selected from zero, 1, 2, and 3.

The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements (including individual variable definitions) of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments. The present invention also provides a pharmaceutical composition comprising a compound of formula I, or an enantiomer, diastereomer, or a pharmaceutically-acceptable salt, and a pharmaceutically acceptable carrier therefore.

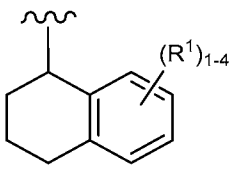
In one non-limiting embodiment, $(CR^4R^4)_{0-1}$ is $(CHR^4)_1$, R_4 is C_{1-2} alkyl, ring A is

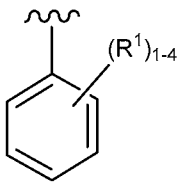


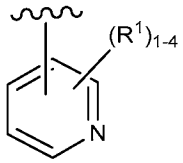
,or


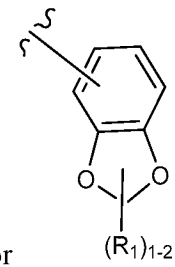
; ring B is


,

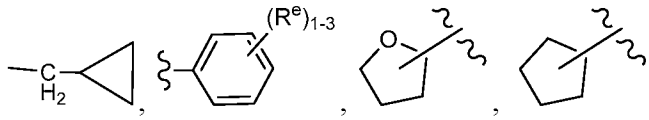
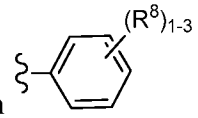
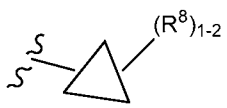
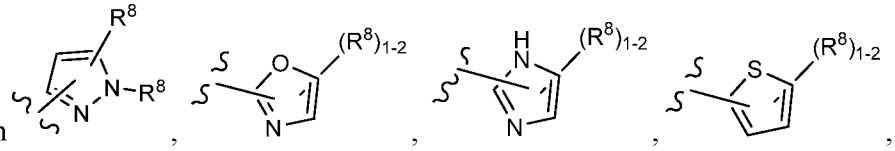
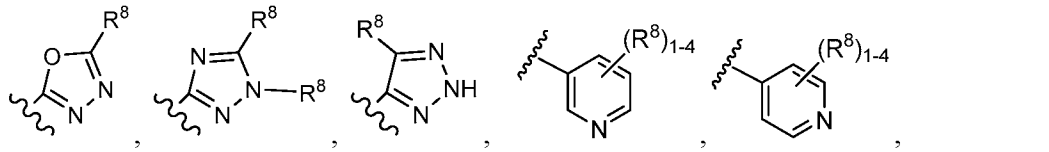
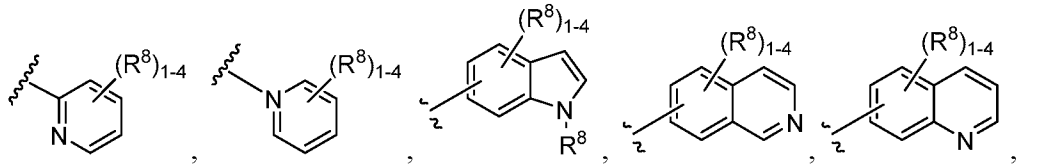
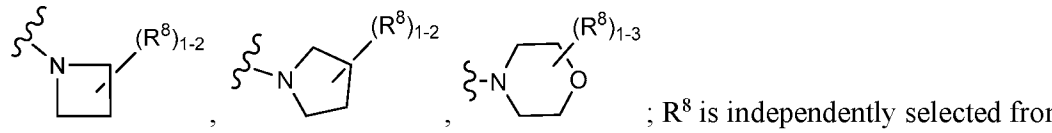


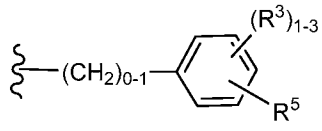
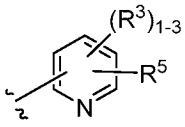
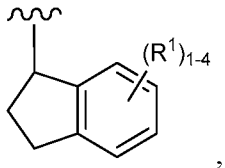
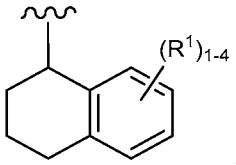
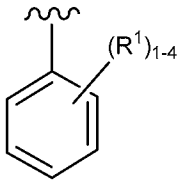
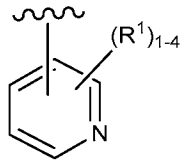
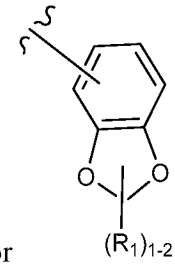
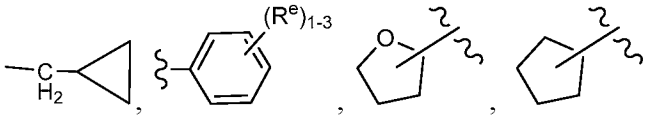
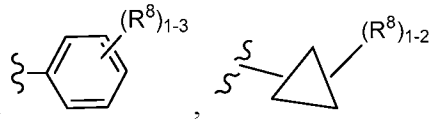
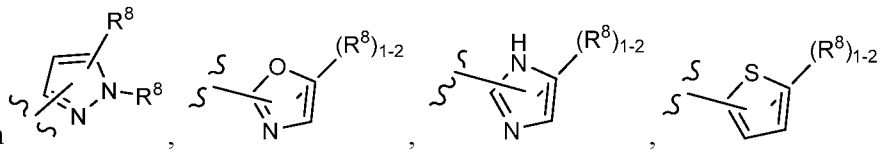
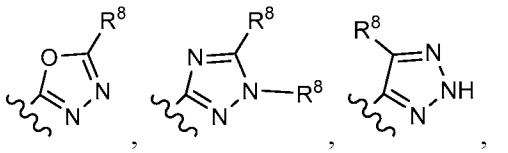
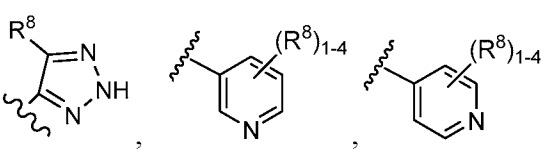
,


,


, or


; R^1 is H, OC_{1-4} alkyl, CN, F, or Cl; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,


, -CH_2OCH_3, -$CH_2OCH_2CH_3$, and -$CH_2OCH(CH_3)_2$; R^3 is H, F, Cl, Br, -C(=O)OR^b, and -C(=O)NHR^a; R^5 is independently selected from R^6, -C(=O)R^6, -C(=O)NHR^6, and -NHC(O)R^6; R^6 is independently selected from carbocyclyl selected from 
, 
, and heterocyclyl selected from 



; R^8 is independently selected from H, F, Cl, Br, CN, -OR^b, -$(CH_2)_nC(=O)R^b$, -$(CH_2)_nC(=O)OR^b$, -$(CH_2)_nC(=O)NR^aR^a$, -$(CH_2)_nNR^aR^a$, -$(CH_2)_nNR^aC(=O)R^b$, -$(CH_2)_nNR^aC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e; R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e; R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e; R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and n is independently selected from zero, 1, 2, and 3.

In another non-limiting embodiment, $(CR^4R^4)_{0-1}$ is absent, R_4 is C_{1-2} alkyl, ring A is  ,or  ; ring B is  ,  ,  ,  , or  ; R^1 is H, OC_{1-4} alkyl, CN, F, or Cl; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  , $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$; R^3 is H, F, Cl, Br, $-C(=O)OR^b$, and $-C(=O)NHR^a$; R^5 is independently selected from R^6, $-C(=O)R^6$, $-C(=O)NHR^6$, and $-NHC(O)R^6$; R^6 is independently selected from carbocyclyl selected from  , and heterocyclyl selected from  ,  ,  ; R^8 is independently selected from H, F, Cl, Br, CN, $-OR^b$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nC(=O)NR^aR^a$,

$-(CH_2)_nNR^aR^a$, $-(CH_2)_nNR^aC(=O)R^b$, $-(CH_2)_nNR^aC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e; R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e; R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e; R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and n is independently selected from zero, 1, 2, and 3.

In another embodiment, the compounds of the present invention have EC_{50} values ≤ 10 μM, using the APJ hcAMP assay disclosed herein, preferably, EC_{50} values ≤ 5 μM, more preferably, EC_{50} values ≤ 1 μM, even more preferably, EC_{50} values ≤ 0.5 μM, even more preferably, EC_{50} values ≤ 0.1 μM, even more preferably, EC_{50} values ≤ 0.01 μM.

In another aspect, the present invention provides compounds selected from any subset list of compounds exemplified in the present application.

In another aspect, the present invention provides compounds selected from the subset in which the APJ hcAMP EC_{50} potency range is A.

In another aspect, the present invention provides compounds selected from the subset in which the APJ hcAMP EC_{50} potency range is B.

In another aspect, the present invention provides compounds selected from the subset in which the APJ hcAMP EC_{50} potency range is C.

II. OTHER EMBODIMENTS OF THE INVENTION

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

The present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent is, for example, angiotensin converting enzyme (ACE) inhibitor, β-adrenergic receptor blocker, angiotensin II receptor blocker, diuretic, aldosterone antagonist and digitalis compound.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ or apelin activity, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

Examples of diseases or disorders associated with the activity of the APJ and apelin that can be prevented, modulated, or treated according to the present invention include, but are not limited to heart failure such as acute decompensated heart failure (ADHF), atrial fibrillation, coronary artery disease, peripheral vascular disease, atherosclerosis, diabetes, metabolic syndrome, hypertension, pulmonary hypertension, cerebrovascular disorders and the sequelae thereof, cardiovascular disorders, angina, ischemia, stroke, myocardial infarction, acute coronary syndrome, reperfusion injury, angioplastic restenosis, vascular complications of diabetes and obesity.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of heart failure, coronary artery disease, peripheral vascular disease, atherosclerosis, diabetes, metabolic syndrome, hypertension, pulmonary hypertension,

atrial fibrillation, angina, ischemia, stroke, myocardial infarction, acute coronary syndrome, reperfusion injury, angioplastic restenosis, vascular complications of diabetes, obesity, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of heart failure such as ADHF, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of diabetes and obesity, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of hypertension, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of pulmonary hypertension, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of acute coronary syndrome and cardiac ischemia, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically

effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a compound of the present invention for use in therapy.

In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin.

In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin, comprising administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention. Preferably, the second therapeutic agent, for example selected inotropic agent such as β-adrenergic agonist (for example dobutamine).

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin.

Where desired, the compound of the present invention may be used in combination with one or more other types of cardiovascular agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of cardiovascular agents that may be optionally employed in combination with the APJ agonist of the present invention may be one, two, three or more cardiovascular agents administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

The compounds of the present invention may be employed in combination with additional therapeutic agent(s) selected from one or more, preferably one to three, of the following therapeutic agents: anti-hypertensive agents, ACE inhibitors, mineralocorticoid receptor antagonists, angiotensin receptor blockers, calcium channel blockers, β-adrenergic receptor blockers, diuretics, vasorelaxation agents such as nitrates, anti-atherosclerotic agents, anti-dyslipidemic agents, anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-thrombotic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-ischemic agents, calcium channel blockers, anti-obesity agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, cognition promoting agents, appetite suppressants, agents for treating heart failure, agents for treating peripheral arterial disease, agents for treating malignant tumors, and anti-inflammatory agents.

In another embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of the following therapeutic agents in treating heart failure: ACE inhibitors, β-blockers, diuretics, mineralocorticoid receptor antagonists, renin inhibitors, calcium channel blockers, angiotensin II receptor antagonists, nitrates, digitalis compounds, inotropic agents.

The present invention may be embodied in other specific forms without parting from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such

isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For examples, "C_1 to C_{12} alkyl" or "C_{1-12} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12} alkyl groups; "C_4 to C_{18} alkyl" or "C_{4-18} alkyl" (or alkylene), is intended to include C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl

(Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

When the term "hydrocarbon chain" is used, it is intended to include "alkyl", "alkenyl" and "alkynyl", unless otherwise specified.

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

"Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated

aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. For example, "C_3 to C_6 cycloalkyl" or "C_{3-6} cycloalkyl" is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

As used herein, "carbocycle", "carbocyclyl", or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, indanyl, and tetrahydronaphthyl. When the term "carbocycle" is used, it is intended to include "aryl." A bridged ring occurs when

one or more, preferably one to three, carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

"Aryl" groups refer to monocyclic or bicyclic aromatic hydrocarbons, including, for example, phenyl, and naphthyl. Aryl moieties are well known and described, for example, in Lewis, R.J., ed., *Hawley's Condensed Chemical Dictionary*, 15th Edition, John Wiley & Sons, Inc., New York (2007). "C_{6-10} aryl" refers to phenyl and naphthyl.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the

total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl,

triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1*H*-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

Examples of 5- to 6-membered heteroaryls include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n=0-4 and m=0-4) and the like.

When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent.

Such amine protecting groups fitting these criteria include those listed in Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007) and *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is

listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Allen, Jr., L.V., ed., *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", Krosgaard-Larsen, P. et al., eds., *A Textbook of Drug Design and Development*, pp. 113-191, Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and

f) Rautio, J., ed., *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol. 47, Wiley-VCH (2011).

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (2nd Edition, reproduced (2006)); Testa, B. et al., *Hydrolysis*

in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology, VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, 3rd Edition, Academic Press, San Diego, CA (2008).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "µL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "aq" for "aqueous", "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse

phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee" are stereochemical designations familiar to one skilled in the art.

AcOH or HOAc	acetic acid
ACN	acetonitrile
Alk	alkyl
BuLi	butyl lithium
$CDCl_3$	deutero-chloroform
CD_3OD	deutero-methanol
Cs_2CO_3	cesium carbonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM or CH_2Cl_2	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether
HCl	hydrochloric acid
H_2O_2	hydrogen peroxide
DIEA, DIPEA or Hunig's base	diisopropylethylamine
HPLC	high-performance liquid chromatography
LCMS	liquid chromatography mass spectrometry
LG	leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
K_2CO_3	potassium carbonate
K_3PO_4	potassium phosphate
K_2HPO_4	dipotassium phosphate
Me	methyl

MeOH	methanol
$MgSO_4$	magnesium sulfate
N_2	nitrogen
Na_2SO_4	sodium sulfate
NaCl	sodium chloride
Na_2CO_3	sodium carbonate
NH_4Cl	ammonium chloride
$NaHCO_3$	sodium bicarbonate
NH_4OAc	ammonium acetate
OXONE®	potassium peroxymonosulfate
$Pd(OAc)_2$	palladium actate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Pd-XPhosG3	2-Dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhosG3	(2-Dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

Description of analytical LCMS methods:

Method A: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm particles; Mobile Phase A: water with 0.1% TFA; Mobile Phase B: ACN with 0.1% TFA; Gradient: 2-98% B over 1 minute, then a 0.5 minute hold at 98% B; Flow: 0.8 mL/min; Detection: UV at 220 nm.

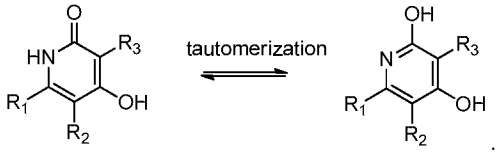
Method B: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm particles; Mobile Phase A: 5:95 ACN:water with 10 mM NH_4OAc; Mobile Phase B: 95:5 ACN:water with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0-100% B over 3

minutes, then a 0.75 minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

Method C: Column: Phenomenex Luna 3u C18(2) 2.0x30mm; Mobile Phase A: 10:90 MeOH:water with 10 mM NH_4OAc; Mobile Phase B: 90:10 MeOH:water with 10 mM NH_4OAc; Temperature: 40 °C; Gradient: 0-100% B over 2 minutes, then a 1 minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

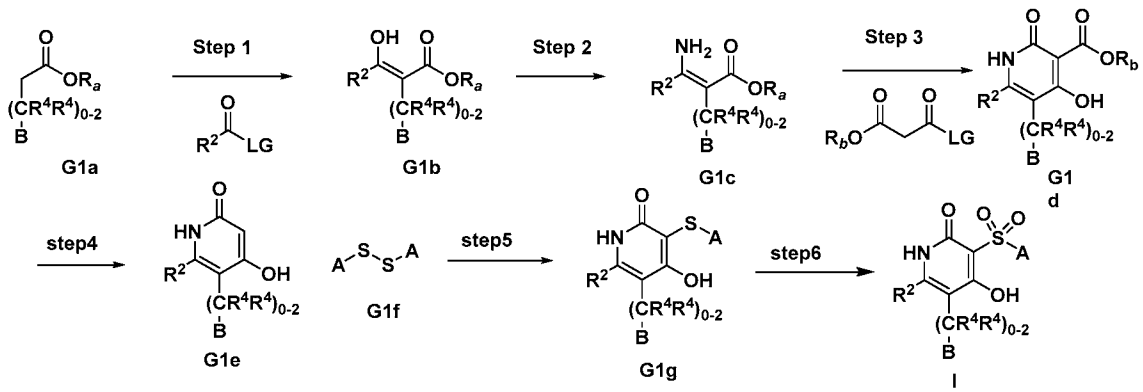
Method D: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm particles; Mobile Phase A: 5:95 ACN:water with 0.1% TFA; Mobile Phase B: 95:5 ACN:water with 0.1% TFA; Temperature: 50°C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

As a person of ordinary skill in the art would be able to understand that a pyridone in a molecule may tautomerize to its keto and enol forms as shown in the following equation, wherein R^1,R^2, R^3 and R^4 are as defined above, this disclosure is intended to cover all possible tautomers even when a structure depicts only one of them.



Generic Schemes

Scheme 1



Step 1 describes the preparation of compounds of Formula G1b by condensing an ester of Formula G1a with an activated acid R^2CO-LG, where LG represents a leaving group (such as halogens and the like). Preferred solvents are ethers (such as tetrahydrofuran, dioxane and the like) and polar aprotic solvents (such as N,N-

dimethylformamide). Preferred bases are metal amides (such as lithium bis(trimethylsilyl)amide and lithium diisopropylamide and the like) and metal hydrides (such as sodium hydride and the like).

Step 2 describes the preparation of compounds of Formula G1c by condensation of compounds of Formula G1b with ammonia. Preferred sources of ammonia are ammonia (gas) or salts thereof (such as ammonium acetate, ammonium formate and the like). Preferred solvents are alcohols (such as methanol, ethanol and the like).

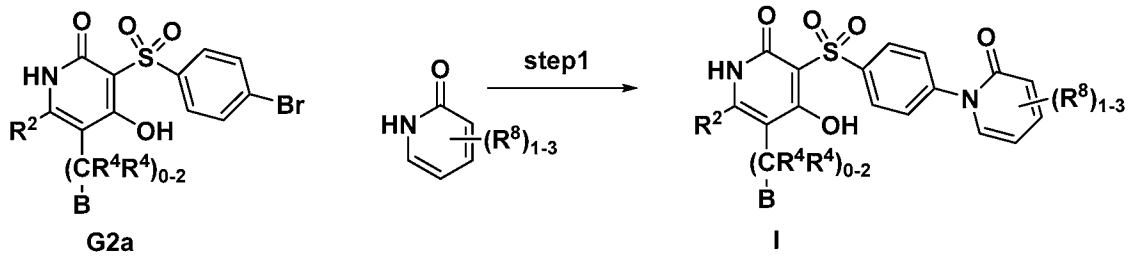
Step 3 describes the preparation of pyridine compounds of Formula G1d from compounds of formula G1c by condensation with malonate derivatives R_bOCOCH_2CO-LG, where LG represents a leaving group (such as halogens and the like or alkoxides such as ethoxide and the like) in the presence of base. The process can be performed in a single step, or two steps. Preferred solvents for the first step of the two step process are halogenated solvents (such as DCM and the like), ethers (such as tetrahydrofuran, dioxane and the like) and water. Preferred bases for the first step of the two step process are tertiary amines (such as TEA, DIEA and the like) and alkaline metal-carbonates, –bicarbonates, -hydroxides (such as sodium carbonate, sodium bicarbonate, sodium hydroxide and the like). Preferred solvents for the second step and for the single step process are alcohols (such as MeOH and EtOH and the like). Preferred bases for the second step and for the single step process are alkaline metal alkoxides (such as sodium ethoxide and the like).

Step 4 describes the preparation of compounds of Formula G1e from a compound of Formula G1d, by decarboxylation by heating in the presence of acid (like HCl). Preferred solvents are inert solvents (such as dioxane)

Step 5 describes the preparation of thioether compounds of Formula G1g from compounds of formula G1e by condensation with disulfide (G1f) under the condition of heating with base. Preferred solvents are protic solvents (like DMF). Preferred bases are alkaline metal-carbonates (such as potassium carbonate).

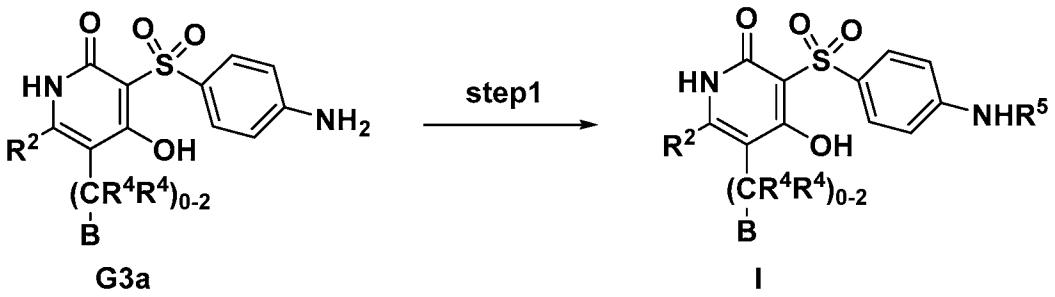
Step 6 describes the preparation of compounds of Formula (I) by oxidation of compounds of Formula G1g to the corresponding sulfone using oxidants (like OXONE® and the like). Preferred solvents are alcohol solvents (such as methanol and the like) and water.

Scheme 2



Step 1 describes the preparation of compounds of Formula (I) by coupling pyridinone with a compound of Formula G2a, by copper catalyzed amination. Preferred catalysts are copper (II) salts (copper (II) acetate and the like). Preferred bases are DBU and the like. Preferred solvents are DMSO and the like.

Scheme 3



Step 1 describes the preparation of compounds of Formula I from a compound of Formula G3a by palladium catalyzed amination, acylation and urea formation. Palladium catalyzed amination involves reaction between aniline and aryl halides. Preferred palladium catalysts are $Pd_2(dba)_3$ and the like. Preferred bases are Cs_2CO_3 and the like. Preferred solvents are dioxane and the like. Acylation involves reaction between aniline and acid chlorides, bases are Hunig's base and the like. Urea formation involves reaction between aniline and isocyanates. Preferred bases are Hunig's base and the like. Preferred solvents are DCM and the like.

IV. BIOLOGY

APJ receptor was discovered in 1993 as an orphan G protein-coupled receptor (GPCR) and was subsequently found to recognize apelin peptide as its endogenous ligand. It belongs to class A of GPCRs and has a classical 7-transmembrane domain structure, exhibiting greatest sequence homology to angiotensin AT1 receptor (for review

see Pitkin, S.L. et al., *Pharmacol. Rev.*, 62(3):331-342 (2010)). APJ is expressed in wide variety of peripheral tissues and the CNS, and has relatively high expression in placenta, myocardium, vascular endothelial cells, smooth muscle cells as well as cardiac myocytes (Kleinz, J.M. et al., *Pharmacol. Ther.*, 107(2):198-211(2005)). Apelin peptide was originally identified in bovine stomach extract and remains to date the only known endogenous ligand and agonist of APJ receptor (Tatemoto, K. et al., *Biochem. Biophys. Res. Commun.*, 255:471-476 (1998)). Tissue expression of apelin gene mirrors closely the APJ expression pattern and has been postulated to act in an autocrine or paracrine manner, often exemplified by reference to "apelin-APJ system". Apelin gene encodes 77 amino acid precursor peptide that is cleaved to form mature secreted peptide undergoing further proteolytic cleavage forming shorter C-terminal fragments. Apelin-36, -17 and -13 represent the major active forms with the pyroglutamated form of apelin-13 being the most stable and the most abundant form present in the cardiac tissue (Maguire, J.J. et al., *Hypertension*, 54(3):598-604 (2009)). Apelin has very short half life in circulation, estimated to be less than 5 minutes (Japp, A.G. et al., *Circulation*, 121(16):1818-1827 (2010)).

Activation of APJ receptor is known to inhibit forskolin-stimulated cyclic AMP (cAMP) levels in pertussis toxin-sensitive manner, indicating coupling to the Gi proteins. The binding affinity of apelin and the EC_{50} values in the cAMP assay are reported to be in the sub-nanomolar range (for review see Pitkin, S.L. et al., *Pharmacol. Rev.*, 62(3):331-342(2010)). In addition to cAMP inhibition, APJ receptor activation also leads to β-arrestin recruitment, receptor internalization and activation of extracellular -regulated kinases (ERKs) (for review see Kleinz, J.M. et al., *Pharmacol. Ther.*,107(2):198-211 (2005)). Which of these signaling mechanisms contribute to modulation of downstream physiological effects of apelin is not clear at present. APJ receptor has been shown to interact with the AT1 receptor. While apelin does not bind AT1 and angiotensin II does not bind APJ, it has been postulated that certain physiological actions of apelin are mediated, at least in part, via functional antagonism of the angiotensin II and AT1 receptor pathway (Chun, A.J. et al., *J. Clin. Invest.*, 118(10):3343-3354 (2008)).

It is also desirable and preferable to find compounds with advantageous and improved characteristics compared with known HF treatment agents, in one or more of the following categories that are given as examples, and are not intended to be limiting:

(a) pharmacokinetic properties, including oral bioavailability, half life, and clearance; (b) pharmaceutical properties; (c) dosage requirements; (d) factors that decrease blood drug concentration peak-to-trough characteristics; (e) factors that increase the concentration of active drug at the receptor; (f) factors that decrease the liability for clinical drug-drug interactions; (g) factors that decrease the potential for adverse side-effects, including selectivity versus other biological targets; and (h) improved therapeutic index.

As used herein, the term "patient" encompasses all mammalian species.

As used herein, the term "subject" refers to any human or non-human organism that could potentially benefit from treatment with an APJ agonist. Exemplary subjects include human beings of any age with risk factors for development of heart failure and the sequelae thereof, angina, ischemia, cardiac ischemia, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia, stroke, as well as atherosclerosis, coronary artery disease, acute coronary syndrome, and/or dyslipidemias.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state.

As used herein, "prophylaxis" or "prevention" cover the preventive treatment of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

As used herein, "risk reduction" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and secondary prevention therapies are examples of risk reduction.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in

combination to modulate APJ and/or to prevent or treat the disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

Intracellular cAMP Accumulation Assay

HEK293 cells stably expressing human APJ receptor were used to assess the activity of compounds. Cultured cells were detached and resuspended in the cAMP Homogeneous Time-Resolved Fluorescence (HTRF) assay buffer (Cisbio cat; #62AM4PEJ). The assay was performed in 384-well assay plates (Perkin-Elmer; cat #6008289) according to assay protocol provided by the manufacturer. Serial dilutions of a compound together with assay buffer containing 0.2nM IBMX and 2 μM forskolin were added to each well containing 5,000 cells and incubated for 30 minutes at room temperature. Subsequently, cAMP D2 reagent was added in the lysis buffer followed by the EuK antibody (Cisbio; cat #62AM4PEJ) and incubated for 60 min. The fluorescence emission ratio was measured using fluorometer. The intracellular cAMP concentrations (compound-stimulated inhibition of forskolin-mediated cAMP production) were calculated by extrapolation from a standard curve using known cAMP concentrations. The EC_{50} values were obtained by fitting the data to a sigmoidal concentration-response curve with variable slope. The maximal achievable inhibition of forskolin-induced cAMP levels (Y_{max}) for each compound was expressed as relative percentage of inhibition attained using pyroglutamated apelin-13 ((Pyr1)apelin-13) peptide, which was set to 100%.

The examples disclosed below were tested in the APJ *in vitro* assays described above and were found having human APJ cyclic AMP (hcAMP) activity. The EC_{50} value of each compound is presented at the end of the example description.

The compounds of the present invention possess activity as agonists of APJ receptor, and, therefore, may be used in the treatment of diseases associated with APJ activity. Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of heart failure, coronary artery disease, peripheral vascular disease, atherosclerosis, diabetes,

metabolic syndrome and the sequelae of thereof, hypertension, pulmonary hypertension, cerebrovascular disorders, atrial fibrillation, angina, ischemia, stroke, myocardial infarction, acute coronary syndrome, reperfusion injury, angioplastic restenosis, vascular complications of diabetes and obesity.

The biological activity of the exemplified compounds of this invention determined by the assay described above is shown at the end of each example. The APJ cAMP EC_{50} potency ranges are as follows: A = 0.01 - 10 nM; B = 10.01 - 100 nM; C = 100.01 - 300 nM.

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, Jr., L.V. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012),

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 5000 mg per day, preferably between about 0.01 to about 1000 mg per day, and most preferably between about 0.1 to about 250 mg per day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the present invention, alone or in combination with a pharmaceutical carrier. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, agents used in treatment of heart failure or other pharmaceutically active material.

The compounds of the present invention may be employed in combination with other APJ agonists or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: agents for treating heart failure, anti-hypertensive agents, anti-atherosclerotic agents, anti-dyslipidemic agents, anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-thrombotic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-ischemic agents, anti-obesity agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, cognition promoting agents, appetite suppressants, and agents for treating peripheral arterial disease.

The compounds of the present invention may be employed in combination with additional therapeutic agent(s) selected from one or more, preferably one to three, of the

following therapeutic agents in treating heart failure and coronary artery disease: ACE inhibitors, β-blockers, diuretics, mineralocorticoid receptor antagonists, renin inhibitors, calcium channel blockers, angiotensin II receptor antagonists, nitrates, digitalis compounds, inotropic agents and β-receptor agonists, anti-hyperlipidemic agents, plasma HDL-raising agents, anti-hypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors), LXR agonist, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, anti-diabetes agents, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin and fibric acid derivatives.

The compounds of the invention may be used in combination with one or more, preferably one to three, of the following anti-diabetic agents depending on the desired target therapy. Studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen. Examples of anti-diabetic agents include, but are not limited to, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone), and related insulin sensitizers, such as selective and non-selective activators of PPARα, PPARβ and PPARγ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); anti-glucocorticoids; TNFα inhibitors; dipeptidyl peptidase IV (DPP4) inhibitor (such as sitagliptin, saxagliptin),GLP-1 agonists or analogs (such as exenatide), α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretagogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the therapeutic agents discussed above for treating heart failure and atherosclerosis.

The compounds of the invention may be used in combination with one or more, preferably one to three, of the following anti-obesity agents selected from phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3-adrenergic receptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in

treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptor modulators, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the *Physicians' Desk Reference*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients but also to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the APJ receptor and apelin activity. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving APJ and apelin or anti-heart failure activity. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving APJ and apelin.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises a first therapeutic agent, comprising a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent for the treatment and/or prophylaxis of multiple diseases or disorders associated with APJ and apelin. The article of manufacture can further comprise: (d) a second

container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

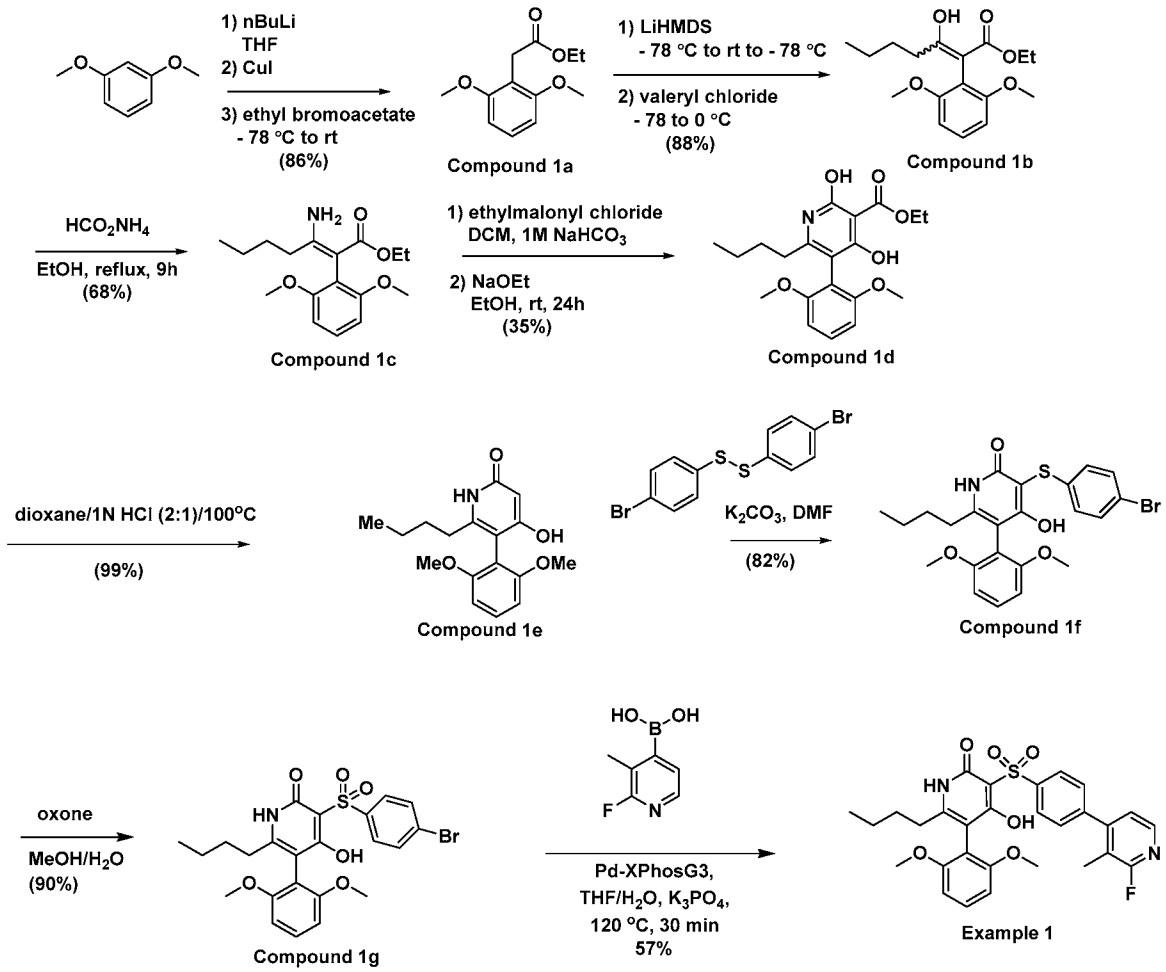
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

VI. EXAMPLES

The following Examples are offered as illustrative, as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

Example 1

6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one



Compound 1a. Ethyl 2-(2,6-dimethoxyphenyl)acetate

To a solution of 1,3-dimethoxybenzene (3.3 mL, 25 mmol) in THF (40 mL) was added dropwise 2.5M nBuLi in hexanes (10 mL, 25 mmol) over a 10 min period then the reaction mixture was stirred for 2h. Crushed copper(I) iodide (2.38 g, 12.5 mmol) was added slowly then the reaction mixture stirred for 1h, turning homogeneous. The reaction mixture was cooled to -78 °C then ethyl bromoacetate (2.8 mL, 25 mmol) was added dropwise over 20 min. The cold bath was removed and the reaction mixture allowed to warm to room temperature. The reaction mixture was quenched by the addition of water then Et_2O added and the mixture filtered through celite. The filtrate was diluted with 1.5N K_2HPO_4 and extracted with Et_2O (2x). The combined organic extracts were washed with brine, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 15% EtOAc/hexanes to give Compound 1a (4.8 g, 86% yield) as a light brown oil which solidified upon standing. MS

m/z = 225.1 (M+H). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23 (t, *J*=8.4 Hz, 1H), 6.58 (d, *J*=8.3 Hz, 2H), 4.17 (q, *J*=7.2 Hz, 2H), 3.83 (s, 6H), 3.71 (s, 2H), 1.27 (t, *J*=7.2 Hz, 3H).

Compound 1b. Ethyl 2-(2,6-dimethoxyphenyl)-3-hydroxyhept-2-enoate

To a solution of Compound 1a (1.50 g, 6.7 mmol) in THF (14 mL) at - 78 °C was added dropwise 1.0M LHMDS in THF (16.7 mL, 16.7 mmol) and the reaction mixture was stirred for 10 min then at room temperature for 1h. The reaction mixture was cooled to - 78 °C then valeryl chloride (1.34 mL, 11.0 mmol) was added dropwise and the mixture allowed to warm to 0 °C and stirred for 15 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 30% EtOAc/hexanes to give an isomeric mixture of Compound 1b (1.80 g, 88 % yield) as a clear colorless oil. MS *m/z* = 309.1 (M+H). ^{1}H NMR of major isomer (400MHz, $CDCl_3$) δ 13.22 (s, 1H), 7.26 - 7.22 (m, 1H), 6.56 (d, *J*=8.6 Hz, 2H), 4.14 (q, *J*=7.0 Hz, 2H), 3.75 (s, 5H), 2.05 - 1.96 (m, 2H), 1.51 - 1.42 (m, 2H), 1.22 - 1.17 (m, 2H), 1.14 (t, *J*=7.2 Hz, 3H), 0.77 (t, *J*=7.3 Hz, 3H).

Compound 1c. Ethyl 3-amino-2-(2,6-dimethoxyphenyl)hept-2-enoate

To a mixture of Compound 1b (1.81 g, 5.90 mmol) and ammonium formate (1.85 g, 29.0 mmol) in absolute ethanol (35 mL) was added molecular sieves then the reaction mixture heated at reflux for 10h. The reaction mixture was allowed to cool to room temperature then filtered and concentrated under reduced pressure. The residue was dissolved in water and extracted with EtOAc (3x). The organic extracts were dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 35% EtOAc/hexanes to give Compound 1c (1.2 g, 68 % yield) as a clear colorless oil. MS *m/z* = 308.1 (M+H). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (t, *J*=8.4 Hz, 1H), 6.55 (d, *J*=8.4 Hz, 2H), 4.05 (q, *J*=7.0 Hz, 2H), 3.75 (s, 6H), 1.98 - 1.88 (m, 2H), 1.43 - 1.31 (m, 2H), 1.18 (dt, *J*=15.0, 7.5 Hz, 2H), 1.09 (t, *J*=7.0 Hz, 3H), 0.73 (t, *J*=7.4 Hz, 3H).

Compound 1d. Ethyl 6-butyl-5-(2,6-dimethoxyphenyl)-2,4-dihydroxynicotinate

To a solution of Compound 1c (1.20 g, 4.0 mmol) in a mixture of DCM (20 mL) and 1N $NaHCO_3$ (24 mL, 24 mmol) was added dropwise a solution of ethyl malonyl chloride (1.54 mL, 12.0 mmol) in DCM (5 mL) and the reaction mixture stirred for 10 min. The mixture was diluted with DCM, the layers separated, and aqueous layer extracted with DCM (2x). The combined extracts were washed with saturated NH_4Cl and brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was dissolved in absolute EtOH (20 mL) then 2.5M sodium ethoxide in ethanol (6.4 mL, 16 mmol) added and the mixture stirred for 24h, generating a precipitate. The reaction mixture was evaporated to dryness then diluted with saturated NH_4Cl and extracted with DCM (3x). The combined extracts were washed with brine, dried (Na_2SO_4), decanted and concentrated under reduced pressure onto celite. The residue was purified by silica gel chromatography eluting with 5 to 75% EtOAc/DCM to give Compound 1d (0.52 g, 35 % yield) as a white solid. MS *m/z* = 376.1 (M+H). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.33 (t, *J*=8.4 Hz, 1H), 6.70 (d, *J*=8.4 Hz, 2H), 4.30 (q, *J*=6.8 Hz, 2H), 3.68 (s, 6H), 2.09 (t, *J*=7.2 Hz, 2H), 1.37 - 1.23 (m, 5H), 1.12 - 0.99 (m, 2H), 0.65 (t, *J*=7.4 Hz, 3H).

Compound 1e. 6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

A mixture of Compound 1d (2 g, 5.33 mmol) in Dioxane (30 mL) and 1N HCl (15 mL) was heated at 100°C for 96 h. The reaction mixture was concentrated, purified by silica gel chromatography to give Compound 1e (1.6 g, 99% yield). MS *m/z* = 304.2 (M+H) (Method A, Rt=0.73 min). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.46 (t, *J*=8.4 Hz, 1H), 6.68 (d, *J*=8.3 Hz, 2H), 6.31 (s, 1H), 3.76 (s, 6H), 2.49 - 2.33 (m, 2H), 1.53 - 1.36 (m, 2H), 1.23 - 1.07 (m, 2H), 0.73 (t, *J*=7.4 Hz, 3H)

Compound 1f. 3-((4-bromophenyl)thio)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

A mixture of Compound 1e (300 mg, 0.99 mmol), 1,2-bis(4-bromophenyl)disulfide (223 mg, 0.59 mmol) and potassium carbonate (205 mg, 1.48 mmol) in DMF (4 mL) was heated at 110°C for 4 h. The reaction mixture was concentrated, diluted with DCM, washed with 1N HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography

to give Compound 1f (400 mg, 82 % yield). MS *m/z* = 490.1 (M+H) (Method A, Rt =1.01 min). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.42 - 7.32 (m, 3H), 7.15 (d, *J*=8.5 Hz, 2H), 6.64 (d, *J*=8.5 Hz, 2H), 3.75 (s, 6H), 2.42 - 2.26 (m, 2H), 1.47 (s, 2H), 1.20 (d, *J*=7.4 Hz, 2H), 0.76 (t, *J*=7.4 Hz, 3H)

Compound 1g. 3-((4-bromophenyl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

To a mixture of 1f (400 mg, 0.82 mmol) in MeOH (24 mL) was added potassium peroxymonosulfate (OXONE,1.0 g, 1.63 mmol) in water (4 mL), and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was concentrated down, diluted with DCM and washed with H_2O. The aqueous layer was re-extracted by DCM twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give Compound 1g (411 mg, 96 % yield) as a yellow solid. MS *m/z* = 524.0 (M+H) (Method A, Rt=1.02 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 11.78 (br. s., 1H), 11.05 (s, 1H), 7.96 (d, *J*=8.5 Hz, 2H), 7.92 - 7.84 (m, 2H), 7.37 (t, *J*=8.3 Hz, 1H), 6.73 (d, *J*=8.5 Hz, 1H), 3.72 (s, 5H), 3.66 (s, 1H), 2.14 - 2.04 (m, 2H), 1.34 - 1.22 (m, 2H), 1.11 - 1.00 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)

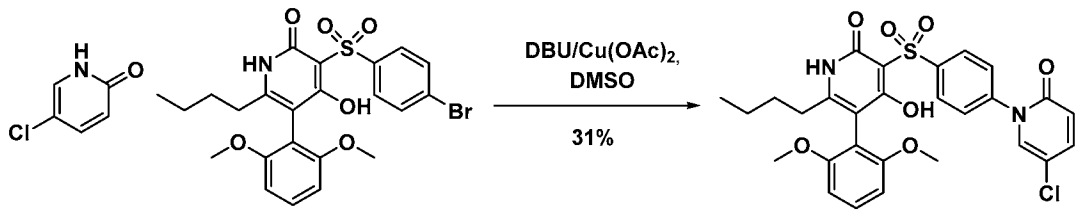
Example 1. 6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one

The mixture of Compound 1g (10 mg, 0.019 mmol), (2-fluoro-3-methylpyridin-4-yl)boronic acid (8.9 mg, 0.057 mmol) and Pd-XPhos G3 (1.22 mg, 0.001 mmol) in THF (1 mL) was added phosphoric acid, potassium salt (0.5 M) (0.077 mL, 0.038 mmol). The reaction mixture was flushed with nitrogen for 5 min and heated in microwave reactor at 120 °C for 30 min. The reaction mixture was concentrated, diluted with DMF and purified by reverse phase HPLC to give Example 1 (6.3 mg, 57% yield). . MS *m/z* = 553.1(M+H) (Method B, Rt=1.87 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.20 - 8.06 (m, 3H), 7.68 (d, *J*=7.3 Hz, 2H), 7.30 (d, *J*=5.2 Hz, 2H), 6.71 (d, *J*=8.2 Hz, 2H), 3.69 (s, 6H), 2.17 (s, 3H), 2.06 (d, *J*=5.5 Hz, 2H), 1.27 (d, *J*=7.3 Hz, 2H), 1.05 (d, *J*=7.3 Hz, 2H), 0.62 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

The following compounds, Example 2 to Example18, were prepared by the general procedures described for Example 1.

Example 19

6-Butyl-3-((4-(5-chloro-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one



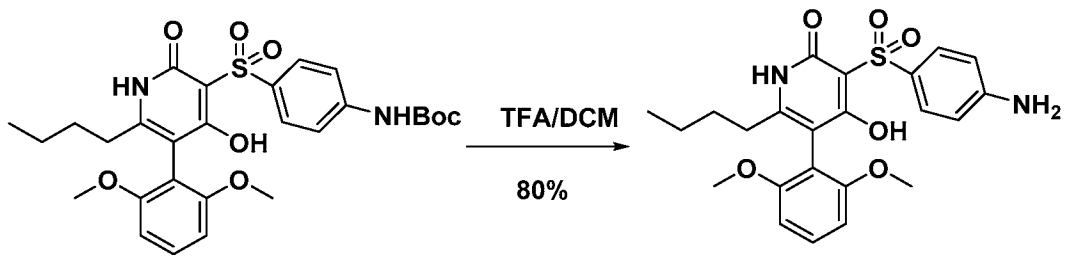
Compound 1g Example 19

A mixture of 5-chloropyridin-2(1H)-one (29.8 mg, 0.23 mmol) and anhydrous copper(II) acetate (20.9 mg, 0.12 mmol) was dissolved in dry DMSO (1.0 mL). Compound 1g (30 mg, 0.057 mmol) and DBU (0.034 mL, 0.23 mmol) were added under nitrogen . The vial was sealed and heated at 130°C for 18 h. The reaction mixture was purified by reverse phase HPLC to give Example 19 (10 mg, 30.5 % yield). MS *m/z* = 571.0 (M+H) (Method A, Rt= 0.95 min). ^{1}H NMR (500MHz, $CDCl_3$) δ11.50 (s, 1H), 8.36 - 8.29 (m, *J*=8.5 Hz, 2H), 7.64 - 7.55 (m, *J*=8.5 Hz, 2H), 7.46 - 7.35 (m, 3H), 6.71 - 6.62 (m, 3H), 3.79 (s, 6H), 2.28 - 2.21 (m, 2H), 1.33 - 1.18 (m, 4H), 0.79 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

The following examples, Example 20 to Example 26, were prepared by the general procedures described for Example 19.

Example 27

3-((4-aminophenyl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

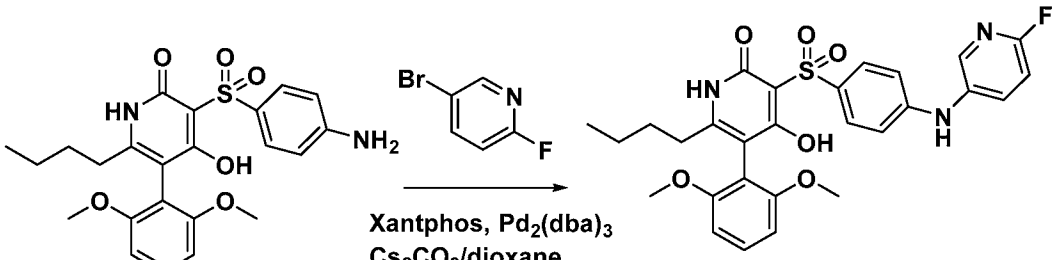


Example 8 Example 27

TFA (0.10 mL, 1.3 mmol) was added to a mixture of Example 8 (4.3 mg, 0.008 mmol) in DCM (1 mL), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase HPLC to give Example 27 (2.8 mg, 80% yield). MS *m/z* = 459.0 (M+H) (Method B, Rt= 1.714 min). ^{1}H NMR (500MHz, DMSO-d$_6$) δ 7.69 - 7.57 (m, *J*=8.5 Hz, 2H), 7.34 (t, *J*=8.3 Hz, 1H), 6.75 - 6.67 (m, *J*=8.4 Hz, 2H), 6.62 (d, *J*=8.6 Hz, 2H), 6.20 (br. s., 2H), 3.69 (s, 5H), 3.46 (br. s., 1H), 2.06 (t, *J*=7.5 Hz, 2H), 1.34 - 1.17 (m, 2H), 1.12 - 0.96 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC$_{50}$ Potency range A.

Example 28

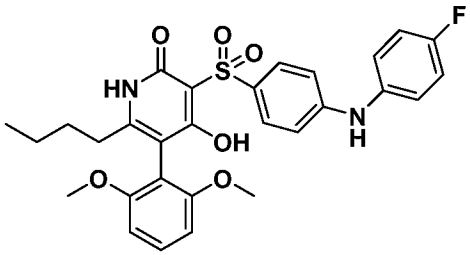
6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-((6-fluoropyridin-3-yl) amino) phenyl) sulfonyl)-4-hydroxypyridin-2(1H)-one



A mixture of Example 27 (10 mg, 0.022mmol) , 5-bromo-2-fluoropyridine (4.22 mg, 0.024 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (2.52 mg, 4.36 µmol), Pd$_2$(dba)$_3$ (2.00 mg, 2.18 µmol) and cesium carbonate (14.2 mg, 0.044 mmol) in dioxane (1 mL) was flushed with nitrogen for 5 min, then heated at 120 °C for 3 h. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to give Example 28 (3.1 mg, 26%). MS *m/z* = 554.2 (M+H) (Method B, Rt= 1.56 min). ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.06 (br. s., 1H), 7.82 (d, *J*=8.6 Hz, 3H), 7.30 (br. s., 1H), 7.15 (d, *J*=6.1 Hz, 1H), 7.09 - 6.96 (m, *J*=8.4 Hz, 2H), 6.77 - 6.56 (m, *J*=8.1 Hz, 2H), 3.66 (s, 2H), 2.55 (s, 4H), 2.01 (br. s., 2H), 1.35 - 1.18 (m, 2H), 1.10 - 0.91 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC$_{50}$ Potency range A.

Example 29

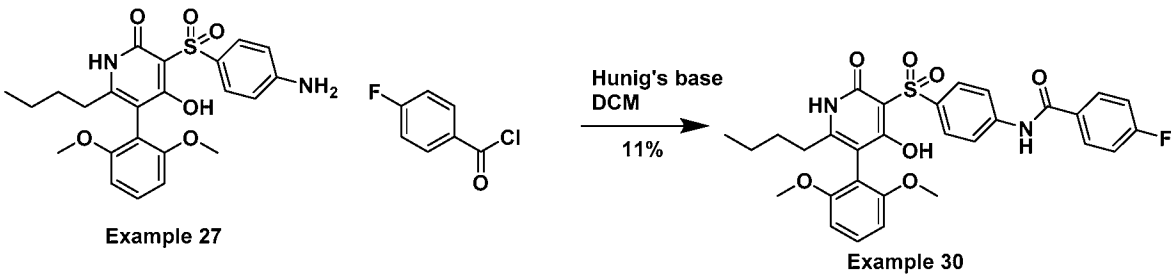
6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-((4-fluorophenyl)amino)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one



Example 29 was prepared from Example 27 using the method described for Example 28. MS *m/z* = 553.1 (M+H) (Method A, Rt= 0.95 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.89 - 7.68 (m, 2H), 7.46 - 7.28 (m, 2H), 7.27 - 7.15 (m, 3H), 7.11 (d, *J*=8.8 Hz, 1H), 7.07 - 6.95 (m, 1H), 6.72 (d, *J*=8.4 Hz, 2H), 3.71 (s, 6H), 2.08 (t, *J*=7.4 Hz, 2H), 1.39 - 1.17 (m, 3H), 1.10 - 0.94 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

Example 30

N-(4-((6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)sulfonyl)phenyl)-4-fluorobenzamide

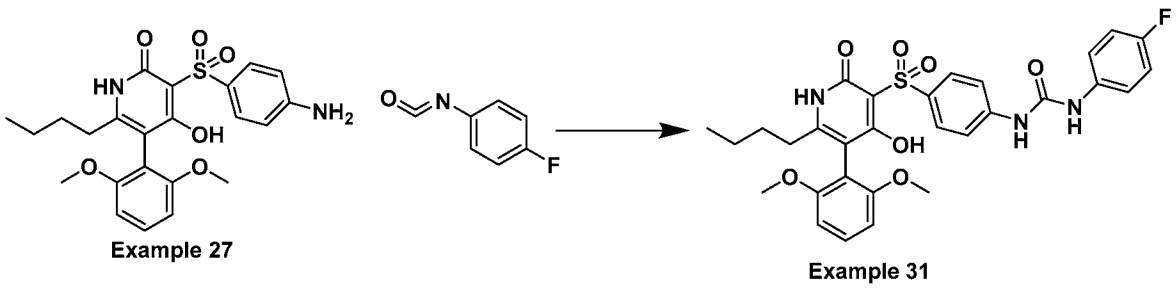


Example 27 Example 30

To a mixture of Example 27 (10 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) was added Hunig's base (5.64 mg, 0.044 mmol) followed by 4-fluorobenzoyl chloride (3.09 µl, 0.026 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to give Example 30 (1.4 mg, 11% yield). MS *m/z* = 581.2 (M+H) (Method D, Rt=2.16 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 10.59 (br. s., 1H), 8.05 (dd, *J*=8.2, 5.7 Hz, 2H), 7.95 (d, *J*=8.5 Hz, 2H), 7.89 (d, *J*=8.2 Hz, 2H), 7.38 (t, *J*=8.7 Hz, 2H), 7.32 - 7.13 (m, 1H), 6.63 (d, *J*=8.2 Hz, 2H), 2.55 (s, 6H), 2.00 - 1.87 (m, 2H), 1.33 - 1.18 (m, 2H), 1.09 - 0.95 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

Example 31

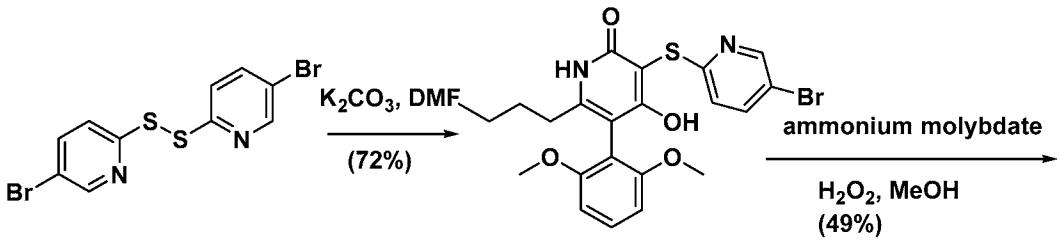
1-(4-((6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)sulfonyl)phenyl)-3-(4-fluorophenyl)urea



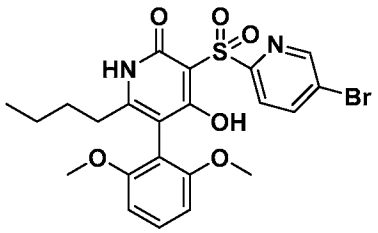
To a mixture of Example 27 (10 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) was added 1-fluoro-4-isocyanatobenzene (4.5 mg, 0.033 mmol) followed by Hunig's base (0.011 mL, 0.065 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to give Example 31 (1.5 mg, 11% yield). MS *m/z* = 596.1 (M+H) (Method B, Rt = 1.76 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.34 (br. s., 1H), 9.01 (s, 1H), 7.99 - 7.83 (m, *J*=8.5 Hz, 2H), 7.70 - 7.57 (m, *J*=8.0 Hz, 2H), 7.47 (dd, *J*=8.4, 5.0 Hz, 2H), 7.33 (br. s., 1H), 7.14 (t, *J*=8.8 Hz, 2H), 6.70 (d, *J*=8.2 Hz, 2H), 3.68 (s, 1H), 3.63 - 3.43 (m, 3H), 2.55 (s, 2H), 2.05 (br. s., 2H), 1.34 - 1.20 (m, 2H), 1.08 - 0.94 (m, 2H), 0.61 (t, *J*=7.2 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

Example 32

3-((5-bromopyridin-2-yl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one



Compound 32a



Example 32

Compound 32a. 3-((5-bromopyridin-2-yl)thio)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

Compound 32a was prepared from 1,2-bis(5-bromopyridin-2-yl)disulfide using the method described for Compound 1f. MS *m/z* = 491.1 (M+H) (Method B, Rt = 1.616 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.92 (d, *J*=6.8 Hz, 1H), 7.32 (t, *J*=8.3 Hz, 1H), 6.80 (d, *J*=8.6 Hz, 1H), 6.70 (d, *J*=8.3 Hz, 2H), 3.70 (s, 6H), 2.11 (t, *J*=7.6 Hz, 2H), 1.43 - 1.26 (m, 2H), 1.16 - 1.00 (m, 2H), 0.66 (t, *J*=7.3 Hz, 3H)

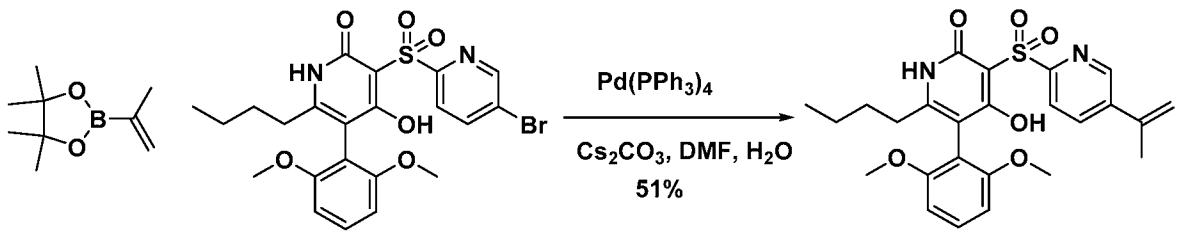
Example 32. 3-((5-bromopyridin-2-yl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

To a mixture of Compound 32a (76 mg, 0.16 mmol) and ammonium molybdate (18 mg, 0.015 mmol) in MeOH (1 mL) was added H_2O_2 (0.035 mL, 50% aq, 0.62 mmol), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase HPLC to give Example 32 (40 mg, 49% yield). MS *m/z* = 523.2 (M+H) (Method B, Rt = 2.00 min). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.83 (br. s., 1H), 8.38 (br. s., 1H), 8.08 (br. s., 1H), 7.32 (br. s., 1H), 6.70 (br. s., 2H), 3.68 (br. s., 6H), 2.05 (br. s., 2H), 1.26 (br. s., 2H), 1.04 (d, *J*=6.4 Hz, 2H), 0.62 (d, *J*=7.0 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

The following compounds, Example 33 to Example 48 were prepared by the general procedures described for Example 32 and Example 1.

Example 49

6-Butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((5-(prop-1-en-2-yl)pyridin-2-yl)sulfonyl)pyridin-2(1H)-one

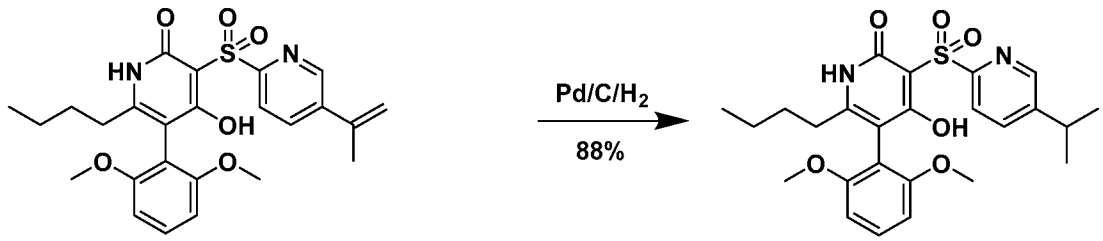


Example 32 Example 49

A mixture of isopropenylboronic acid pinacol ester (7.2 mg, 0.043 mmol), Example 32 (15 mg, 0.029 mmol), $Pd(PPh_4)_3$ (3.31 mg, 2.87 μmol) and cesium carbonate (28.0 mg, 0.086 mmol) in DMF (0.6 mL) and water (0.2 mL) was flushed with nitrogen for 5 min, then heated at 90°C for 3h. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to give Example 49 (7.5 mg, 51%). MS *m/z* = 485.2 (M+H) (Method B, Rt= 1.48 min. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.75 (br. s., 1H), 8.13 (d, *J*=6.5 Hz, 1H), 8.02 (d, *J*=7.2 Hz, 1H), 7.26 (t, *J*=7.5 Hz, 1H), 6.65 (d, *J*=8.1 Hz, 2H), 5.65 (br. s., 1H), 5.33 (br. s., 1H), 3.65 (br. s., 2H), 2.55 (s, 4H), 2.16 (s, 3H), 1.97 (br. s., 2H), 1.31 - 1.18 (m, 2H), 1.15 - 0.93 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H). Human APJ cAMP EC_{50} Potency range A.

Example 50

6-Butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((5-isopropylpyridin-2-yl)sulfonyl)pyridin-2(1H)-one

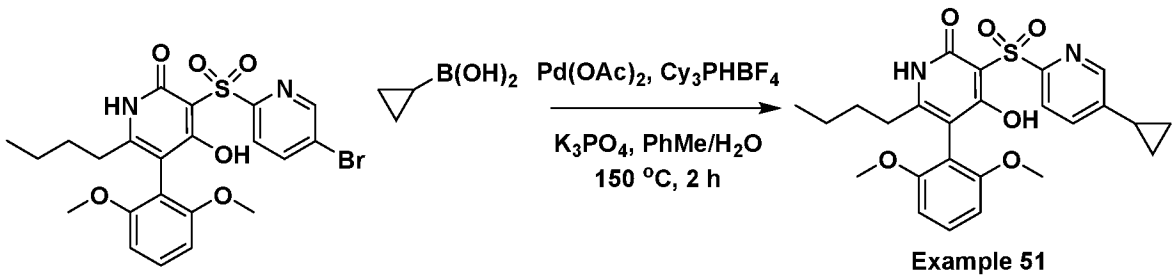


Example 49 Example 50

A mixture of Example 49 (5.3 mg, 11 μmol) and 10% palladium on carbon (11.6 mg, 0.011 mmol) in MeOH (1 mL) was stirred under hydrogen balloon at room temperature for 18 h. The reaction mixture was filtered through celite, concentrated and purified by reverse phase HPLC to give Example 50 (4.7 mg, 88% yield). MS *m/z* = 487.2 (M+H) (Method B, Rt= 1.46 min) ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.63 (s, 1H), 8.10 (d, *J*=8.1 Hz, 1H), 8.04 (d, *J*=7.7 Hz, 1H), 7.36 (t, *J*=8.3 Hz, 1H), 6.74 (d, *J*=8.4 Hz, 2H), 3.72 (s, 6H), 3.13 - 2.97 (m, 1H), 2.19 - 1.99 (m, 2H), 1.37 - 1.15 (m, 8H), 1.10 - 0.96 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC$_{50}$ Potency range A.

Example 51

6-Butyl-3-((5-cyclopropylpyridin-2-yl)sulfonyl)-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one

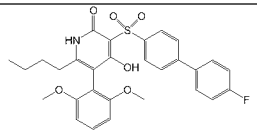
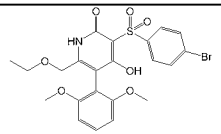
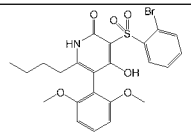
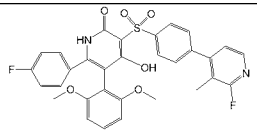


Example 32 (9 mg, 0.02 mmol), cyclopropylboronic acid (8.86 mg, 0.1 mmol), palladium(II) acetate (0.77 mg, 0.003 mmol), tricyclohexylphosphonium tetrafluoroborate (2.53 mg, 6.88 μmol) and phosphoric acid, potassium salt (14.6 mg, 0.069 mmol) were placed in a pressure vial, and the mixture was purged with argon gas three times. Toluene (1.0 mL) and water (0.2 mL) were added, and the reaction mixture was purged with argon.The reaction mixture was heated to 130°C for 2 h, concentrated and purified by reverse phase HPLC to give Example 51 (1.8 mg, 22% yield). MS *m/z* = 485.3 (M+H) (Method B, Rt=1.52 min ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.49 (br. s., 1H), 8.00 (br. s., 1H), 7.75 (br. s., 1H), 7.34 (br. s., 1H), 6.72 (d, *J*=7.2 Hz, 2H), 3.71 (br. s., 2H), 3.55 - 3.31 (m, 4H), 2.17 - 1.93 (m, 3H), 1.32 - 1.25 (m, 2H), 1.12 (d, *J*=7.1 Hz, 2H), 1.09 - 0.96 (m, 2H), 0.93 - 0.78 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H). Human APJ cAMP EC$_{50}$ Potency range A.

Ex #	Structure	Name	HNMR	Rt (min) Method M+H	Human APJ cAMP EC_{50} Potency range)
2		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((4-(2-methoxypyridin-3-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ8.25 (d, *J*=3.7 Hz, 1H), 8.14 - 8.01 (m, *J*=8.2 Hz, 2H), 7.89 - 7.76 (m, 3H), 7.37 (t, *J*=8.2 Hz, 1H), 7.20 - 7.12 (m, 1H), 6.81 - 6.66 (m, *J*=8.5 Hz, 2H), 3.97 - 3.86 (m, 4H), 3.72 (s, 6H), 2.17 - 2.03 (m, 2H), 1.38 - 1.20 (m, 3H), 1.14 - 0.97 (m, 2H), 0.63 (t, *J*=7.2 Hz, 3H)	1.969 B 551.3	A
3		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (br. s., 2H), 8.20 - 8.04 (m, *J*=7.9 Hz, 2H), 7.76 - 7.58 (m, *J*=7.6 Hz, 2H), 7.44 - 7.24 (m, 2H), 6.72 (d, *J*=8.2 Hz, 2H), 3.70 (s, 6H), 2.27 (s, 3H), 2.07 (d, *J*=6.1 Hz, 2H), 1.38 - 1.18 (m, 2H), 1.12 - 0.97 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H)	1.726 B 535.1	A
4		6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-(5-fluoropyridin-3-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 8.88 (br. s., 1H), 8.67 (br. s., 1H), 8.19 (d, *J*=9.8 Hz, 1H), 8.12 (d, *J*=7.6 Hz, 2H), 8.05 (br. s., 2H), 7.34 (br. s., 1H), 6.72 (d, *J*=7.9 Hz, 2H), 3.70 (s, 6H), 2.55 (s, 3H), 2.07 (br. s., 2H), 1.37 - 1.18 (m, 2H), 1.15 - 0.97 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.749 B 539.0	A

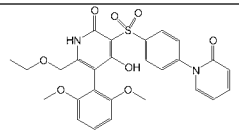
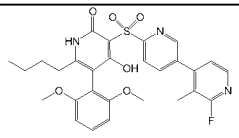
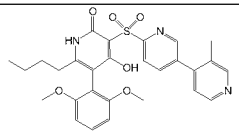
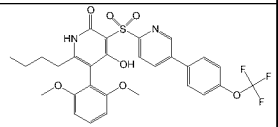
5		6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.16 - 8.04 (m, *J*=8.2 Hz, 2H), 7.90 (t, *J*=8.2 Hz, 1H), 7.75 - 7.61 (m, *J*=7.9 Hz, 2H), 7.34 (t, *J*=8.2 Hz, 1H), 7.12 (dd, *J*=8.1, 2.6 Hz, 1H), 6.71 (d, *J*=8.5 Hz, 2H), 3.70 (s, 6H), 2.40 (s, 3H), 2.07 (t, *J*=7.3 Hz, 2H), 1.36 - 1.20 (m, 2H), 1.11 - 0.98 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	1.746 B 553.2	A
6		6-butyl-5-(2,6-dimethoxyphenyl)-3-((4-(6-fluoropyridin-3-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.65 (br. s., 1H), 8.39 (br. s., 1H), 8.20 - 8.05 (m, *J*=7.9 Hz, 2H), 8.04 - 7.91 (m, *J*=7.9 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 6.72 (d, *J*=8.2 Hz, 2H), 3.70 (s, 6H), 2.07 (d, *J*=5.8 Hz, 2H), 1.36 - 1.20 (m, 2H), 1.11 - 0.90 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.679 B 539.2	A
7		6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 7.91 - 7.80 (m, *J*=8.1 Hz, 2H), 7.41 - 7.22 (m, 3H), 6.79 - 6.63 (m, *J*=8.3 Hz, 2H), 3.69 (s, 6H), 2.05 (d, *J*=3.8 Hz, 3H), 1.35 - 1.16 (m, 2H), 1.14 - 0.95 (m, 4H), 0.80 (d, *J*=4.4 Hz, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	2.130 C 484.3	A
8		tert-butyl (4-((6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)sulfonyl)phenyl)carbamate	^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.88 (br. s., 1H), 7.96 - 7.82 (m, *J*=8.2 Hz, 2H), 7.63 (d, *J*=7.2 Hz, 2H), 7.43 - 7.26 (m, 1H), 6.79 - 6.60 (m, *J*=8.2 Hz, 2H), 2.51 (br. s., 6H), 2.04 (br. s., 2H), 1.48 (s, 9H), 1.33 - 1.16 (m, 2H), 1.08 - 0.94 (m, 2H), 0.61 (t, *J*=7.2 Hz, 3H)	2.007 B 559.1	A

9		5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-3-((4'-fluoro-[1,1'-biphenyl]-4-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.14 - 7.99 (m, *J*=8.1 Hz, 2H), 7.89 (d, *J*=7.2 Hz, 2H), 7.84 - 7.71 (m, 2H), 7.35 (t, *J*=8.7 Hz, 3H), 6.82 - 6.65 (m, *J*=8.2 Hz, 2H), 3.87 (s, 1H), 3.44 (br. s., 1H), 3.23 (q, *J*=6.9 Hz, 2H), 2.55 (s, 6H), 0.96 (t, *J*=6.9 Hz, 3H)	1.500 B 540.4	A
10		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-(phenylsulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.07 - 7.93 (m, *J*=7.6 Hz, 2H), 7.71 (br. s., 1H), 7.63 (br. s., 2H), 7.34 (br. s., 1H), 6.80 - 6.64 (m, *J*=8.2 Hz, 2H), 3.70 (s, 6H), 2.07 (br. s., 2H), 1.34 - 1.17 (m, 2H), 1.12 - 0.95 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H)	1.709 B 444.2	A
11		3-((4-cyclopropylphenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 7.91 - 7.84 (m, *J*=8.3 Hz, 2H), 7.37 (t, *J*=8.4 Hz, 1H), 7.34 - 7.28 (m, *J*=8.3 Hz, 2H), 6.73 (d, *J*=8.4 Hz, 2H), 3.89 (s, 2H), 3.71 (s, 6H), 3.22 (q, *J*=6.9 Hz, 2H), 2.04 (br. s., 1H), 1.08 (d, *J*=6.3 Hz, 2H), 0.95 (t, *J*=7.0 Hz, 3H), 0.81 (d, *J*=4.6 Hz, 2H)	0.99 A 486.2	A
12		5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-3-((4-(6-fluoropyridin-3-yl)phenyl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.59 (br. s., 1H), 8.33 (t, *J*=7.0 Hz, 1H), 8.12 - 7.98 (m, *J*=8.0 Hz, 2H), 7.92 - 7.80 (m, *J*=7.5 Hz, 2H), 7.38 - 7.21 (m, 2H), 6.66 (d, *J*=8.2 Hz, 2H), 3.72 (br. s., 4H), 3.63 (s, 2H), 3.22 (q, *J*=6.9 Hz, 2H), 2.55 (s, 2H), 0.96 (t, *J*=6.9 Hz, 3H)	1.309 B 541.3	A

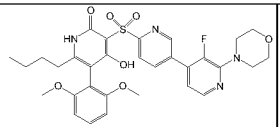
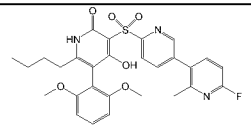
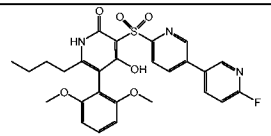
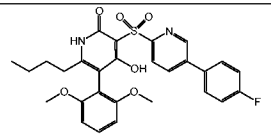
13		6-butyl-5-(2,6-dimethoxyphenyl)-3-((4'-fluoro-[1,1'-biphenyl]-4-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 7.82 (br. s., 3H), 7.76 (br. s., 3H), 7.37 - 7.19 (m, 3H), 6.66 (br. s., 2H), 3.68 (br. s., 4H), 3.53 (br. s., 2H), 2.01 (br. s., 2H), 1.37 - 1.14 (m, 2H), 1.14 - 0.93 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.07 A 538.2	B
14		3-((4-bromophenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, CHLOROFORM-d) δ 11.50 (s, 1H), 8.08 - 7.95 (m, 2H), 7.74 - 7.62 (m, 2H), 7.37 (t, *J*=8.4 Hz, 1H), 6.63 (d, *J*=8.3 Hz, 2H), 4.06 (s, 2H), 3.76 (s, 6H), 3.45 (q, *J*=6.9 Hz, 2H), 1.17 (t, *J*=6.9 Hz, 3H)	1.916 D 523.9	B
15		3-((2-bromophenyl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.09 (d, *J*=7.3 Hz, 1H), 7.64 (d, *J*=6.7 Hz, 1H), 7.48 (br. s., 1H), 7.38 (br. s., 1H), 7.18 (t, *J*=8.1 Hz, 1H), 6.58 (d, *J*=8.2 Hz, 2H), 3.58 (s, 6H), 1.34 - 1.15 (m, 2H), 1.11 - 0.94 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	1.776 B 522.1	B
16		5-(2,6-dimethoxyphenyl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(4-fluorophenyl)-4-hydroxypyridin-2(1H)-one	1H NMR (500MHz, DMSO-d6) δ 8.14 (d, *J* = 4.9 Hz, 2H), 7.65 (d, *J* = 5.8 Hz, 2H), 7.30 (d, *J* = 4.9 Hz, 1H), 7.07-7.16 (m, 4H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.49 (d, *J* = 8.2 Hz, 2H), 3.54 (s, 6H), 2.18 (s, 3H)	1.638 B 591.3	A

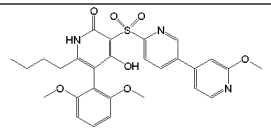
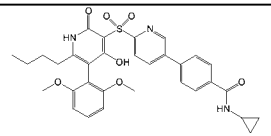
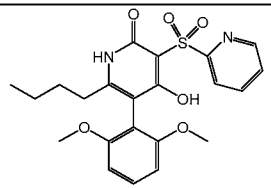
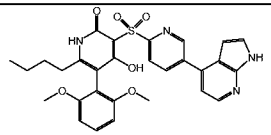
17		5-(2,6-dimethoxyphenyl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(4-fluorophenyl)-4-hydroxypyridin-2(1H)-one	1H NMR (500MHz, DMSO-d6) δ8.14 (d, *J* = 5.7 Hz, 2H), 7.90 (t, *J* = 7.8 Hz, 1H), 7.67 (br s, 2H), 7.09-7.20 (m, 4H), 7.04 (t, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 7.5 Hz, 2H), 3.48 (s, 6H), 2.55 (s, 3H)	1.528 B 591.1	A
18		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((1-hydroxy-1l4-pyridin-2-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 7.79 (br. s., 1H), 7.41 (t, *J*=7.4 Hz, 1H), 7.05 (t, *J*=8.4 Hz, 1H), 6.82 - 6.71 (m, 1H), 6.38 (d, *J*=8.4 Hz, 2H), 6.32 (d, *J*=7.6 Hz, 1H), 3.55 - 3.38 (m, 2H), 2.55 (s, 4H), 2.20 (br. s., 2H), 1.40 (br. s., 2H), 1.19 - 0.97 (m, 2H), 0.67 (br. s., 3H)	1.327 D 461.1	C
20		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((4-(5-methyl-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.12 (br. s., 2H), 7.64 (br. s., 2H), 7.52 (br. s., 1H), 7.44 (d, *J*=8.5 Hz, 1H), 7.28 (br. s., 1H), 6.65 (br. s., 2H), 6.48 (d, *J*=8.5 Hz, 1H), 3.65 (br. s., 3H), 3.58 - 3.42 (m, 6H), 2.06 (br. s., 2H), 1.22 (br. s., 2H), 1.00 (br. s., 2H), 0.59 (br. s., 3H)	1.387 B 551.9	A
21		3-((4-(5-chloro-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.10 - 8.02 (m, *J*=8.0 Hz, 2H), 7.99 (d, *J*=2.4 Hz, 1H), 7.64 - 7.51 (m, 3H), 7.25 (br. s., 1H), 6.69 - 6.59 (m, *J*=8.2 Hz, 2H), 6.55 (d, *J*=9.8 Hz, 1H), 3.78 (s, 1H), 3.63 (s, 2H), 3.24 (d, *J*=7.0 Hz, 1H), 2.55 (s, 6H), 0.98 (t, *J*=6.9 Hz, 3H)	1.106 B 574.1	A

22		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((4-(2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.19 - 8.09 (m, *J*=8.5 Hz, 2H), 7.76 - 7.65 (m, 3H), 7.60 - 7.50 (m, 1H), 7.36 (t, *J*=8.4 Hz, 1H), 6.78 - 6.67 (m, *J*=8.2 Hz, 2H), 6.53 (d, *J*=9.2 Hz, 1H), 6.39 (t, *J*=6.6 Hz, 1H), 2.55 (s, 6H), 2.17 - 1.96 (m, 2H), 1.39 - 1.15 (m, 2H), 1.13 - 0.94 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H)	1.278 B 537.0	A
23		3-((4-(5-chloro-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-6-(4-fluorophenyl)-4-hydroxypyridin-2(1H)-one	1H NMR (500MHz, DMSO-d6) d 8.14 (d, J = 7.7 Hz, 2H), 8.04 (br s, 2H), 7.56-7.68 (m, 3H), 7.07-7.15 (m, 2H), 6.98-7.04 (m, 2H), 6.57 (d, *J* = 9.9 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 2H), 3.53 (s, 6H)	1.428 B 609.1	A
24		5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxy-3-((4-(5-methyl-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.20 - 8.09 (m, *J*=8.4 Hz, 2H), 7.75 - 7.62 (m, *J*=8.5 Hz, 2H), 7.52 (br. s., 1H), 7.45 (d, *J*=9.2 Hz, 1H), 7.37 (t, *J*=8.3 Hz, 1H), 6.73 (d, *J*=8.4 Hz, 2H), 6.48 (d, *J*=9.3 Hz, 1H), 3.90 (s, 1H), 3.68 (br. s., 1H), 3.22 (q, *J*=6.9 Hz, 2H), 2.55 (s, 6H), 2.05 (s, 3H), 0.95 (t, *J*=6.9 Hz, 3H)	1.601 B 553.1	A
25		3-((4-(3,5-dichloro-2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)-5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.36 (s, 1H), 8.21 (br. s., 1H), 8.07 (br. s., 2H), 7.93 (s, 1H), 7.50 (br. s., 1H), 7.42 (br. s., 1H), 7.35 (br. s., 1H), 6.71 (d, *J*=7.3 Hz, 2H), 3.88 (br. s., 1H), 3.69 (br. s., 1H), 3.30 - 3.18 (m, 2H), 2.55 (s, 6H), 0.96 (t, *J*=6.3 Hz, 3H)	1.604 B 606.9	B

26		5-(2,6-dimethoxyphenyl)-6-(ethoxymethyl)-4-hydroxy-3-((4-(2-oxopyridin-1(2H)-yl)phenyl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.22 - 8.08 (m, *J*=8.2 Hz, 2H), 7.76 - 7.65 (m, 3H), 7.56 (t, *J*=7.8 Hz, 1H), 7.37 (t, *J*=8.2 Hz, 1H), 6.81 - 6.65 (m, *J*=8.2 Hz, 2H), 6.53 (d, *J*=9.2 Hz, 1H), 6.38 (t, *J*=6.7 Hz, 1H), 3.90 (s, 2H), 3.71 (s, 5H), 3.56 (d, *J*=5.5 Hz, 1H), 3.23 (q, *J*=6.9 Hz, 2H), 0.96 (t, *J*=7.0 Hz, 3H)	0.81 A 539.0	A
33		6-butyl-5-(2,6-dimethoxyphenyl)-3-((2'-fluoro-3'-methyl-[3,4'-bipyridin]-6-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.62 (br. s., 1H), 8.16 (d, *J*=5.0 Hz, 1H), 8.09 (br. s., 2H), 7.33 (d, *J*=4.9 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 6.59 (d, *J*=8.2 Hz, 2H), 2.55 (s, 6H), 2.22 - 2.08 (m, 3H), 1.91 (s, 2H), 1.08 - 0.96 (m, 2H), 0.85 (t, *J*=6.7 Hz, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.526 B 554.3	A
34		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((3'-methyl-[3,4'-bipyridin]-6-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.63 (br. s., 2H), 8.10 (br. s., 2H), 7.36 (br. s., 1H), 7.21 (br. s., 1H), 6.61 (d, *J*=7.7 Hz, 2H), 2.55 (s, 6H), 2.28 (br. s., 3H), 1.91 (s, 2H), 1.35 - 1.18 (m, 2H), 1.11 - 0.90 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H)	1.273 B 536.0	A
35		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((5-(4-(trifluoromethoxy)phenyl)pyridin-2-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.99 (br. s., 1H), 8.40 (br. s., 1H), 8.22 (br. s., 1H), 8.03 - 7.86 (m, *J*=8.3 Hz, 2H), 7.60 - 7.44 (m, *J*=8.2 Hz, 2H), 7.32 (br. s., 1H), 6.70 (d, *J*=7.3 Hz, 2H), 2.51 (br. s., 6H), 2.05 (br. s., 2H), 1.34 - 1.18 (m, 2H), 1.11 - 0.95 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H)	1.10 A 605.0	A

36		6-butyl-5-(2,6-dimethoxyphenyl)-3-((5-(4-fluoro-2-methylphenyl)pyridin-2-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.70 (br. s., 1H), 8.21 (br. s., 1H), 8.16 (br. s., 1H), 7.45 - 7.31 (m, 2H), 7.26 (d, *J*=8.2 Hz, 1H), 7.18 (t, *J*=8.4 Hz, 1H), 6.71 (br. s., 2H), 2.55 (s, 6H), 2.31 - 2.20 (m, 3H), 2.07 (d, *J*=7.3 Hz, 2H), 1.39 - 1.16 (m, 2H), 1.13 - 0.95 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.817 B 553.1	A
37		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((5-(o-tolyl)pyridin-2-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.63 (br. s., 1H), 8.23 - 8.03 (m, 2H), 7.43 - 7.19 (m, 5H), 6.67 (d, *J*=8.3 Hz, 2H), 3.66 (s, 3H0, 2.55 (s, 3H), 2.30 - 2.17 (m, 3H), 2.06 - 1.94 (m, 2H), 1.34 - 1.18 (m, 3H), 1.12 - 0.94 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	2.181 B 535.1	A
38		6-butyl-5-(2,6-dimethoxyphenyl)-3-((5-(3-fluoro-2-methylphenyl)pyridin-2-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.73 (br. s., 1H), 8.18 (s, 1H), 8.22 (s, 1H), 7.45 - 7.34 (m, 1H), 7.34 - 7.26 (m, 2H), 7.22 (d, *J*=7.4 Hz, 1H), 6.72 (d, *J*=7.7 Hz, 2H), 3.71 (br. s., 3H), 3.38 (br. s., 3H), 2.15 (s, 3H), 2.07 (br. s., 2H), 1.36 - 1.24 (m, 2H), 1.13 - 0.97 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	1.817 B 553.1	A
39		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((5-methylpyridin-2-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (600MHz, DMSO-d$_6$) δ 8.53 (br. s., 1H), 8.06 (d, *J*=7.1 Hz, 1H), 7.95 (br. s., 1H), 7.42 - 7.27 (m, 1H), 6.72 (d, *J*=8.1 Hz, 2H), 3.72 (s, 3H), 3.51 - 3.33 (m, 3H), 2.41 (s, 3H), 2.07 (br. s., 2H), 1.28 (quin, *J*=7.4 Hz, 2H), 1.05 (sxt, *J*=7.3 Hz, 2H), 0.63 (t, *J*=7.4 Hz, 3H)	0.92 A 459.0	A

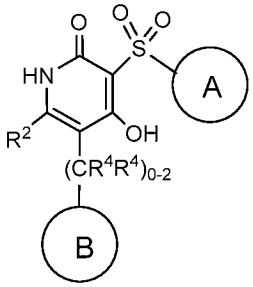
40		6-butyl-5-(2,6-dimethoxyphenyl)-3-((3'-fluoro-2'-morpholino-[3,4'-bipyridin]-6-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.85 (br. s., 1H), 8.30 (d, *J*=7.9 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 8.14 (d, *J*=5.0 Hz, 1H), 7.26 (t, *J*=8.2 Hz, 1H), 7.14 (t, *J*=4.8 Hz, 1H), 6.65 (d, *J*=8.3 Hz, 2H), 3.90 (s, 1H), 3.83 - 3.69 (m, 3H), 3.65 (s, 3H), 3.41 (d, *J*=4.3 Hz, 1H), 2.51 (br. s., 6H), 2.04 - 1.93 (m, 2H), 1.33 - 1.23 (m, 2H), 1.12 - 0.95 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.353 B 625.3	A
41		6-butyl-5-(2,6-dimethoxyphenyl)-3-((6'-fluoro-2'-methyl-[3,3'-bipyridin]-6-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.68 (br. s., 1H), 8.15 (br. s., 2H), 7.96 (t, *J*=8.2 Hz, 1H), 7.27 (br. s., 1H), 7.22 - 7.11 (m, 1H), 6.66 (d, *J*=8.4 Hz, 2H), 3.66 (s, 3H), 2.55 (s, 3H), 2.40 (s, 3H), 1.99 (br. s., 2H), 1.34 - 1.25 (m, 2H), 1.19 - 0.97 (m, 3H), 0.85 (t, *J*=6.8 Hz, 1H), 0.63 (t, *J*=7.3 Hz, 3H)	1.403 B 554.1	A
42		6-butyl-5-(2,6-dimethoxyphenyl)-3-((6'-fluoro-[3,3'-bipyridin]-6-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.06 (br. s., 1H), 8.71 (br. s., 1H), 8.53 - 8.38 (m, 2H), 8.25 (d, *J*=7.8 Hz, 1H), 7.45 - 7.27 (m, 2H), 6.73 (d, *J*=8.2 Hz, 2H), 3.65 (s, 2H), 3.59 (br. s., 4H), 2.08 (br. s., 2H), 1.26 (dd, *J*=15.1, 7.7 Hz, 2H), 1.11 - 0.93 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H)	1.911 D 540.2	A
43		6-butyl-5-(2,6-dimethoxyphenyl)-3-((5-(4-fluorophenyl)pyridin-2-yl)sulfonyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.01 (br. s., 1H), 8.40 (br. s., 1H), 8.22 (br. s., 1H), 7.96 - 7.81 (m, 2H), 7.46 - 7.24 (m, 3H), 6.72 (d, *J*=7.7 Hz, 2H), 3.71 (m, 5H), 2.55 (s, 1H), 2.07 (br. s., 2H), 1.36 - 1.25 (m, 2H), 1.12 - 0.94 (m, 2H), 0.62 (t, *J*=7.3 Hz, 3H)	1.673 B 539.3	A

44		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-((2'-methoxy-[3,4'-bipyridin]-6-yl)sulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.90 (s, 1H), 8.38 - 8.27 (m, 2H), 8.02 (d, *J*=8.2 Hz, 1H), 7.39 (d, *J*=4.7 Hz, 1H), 7.22 (s, 1H), 7.18 - 7.10 (m, 1H), 6.55 (d, *J*=8.3 Hz, 2H), 3.91 (s, 3H), 2.55 (s, 6H), 1.87 - 1.80 (m, 2H), 1.34 - 1.17 (m, 2H), 1.09 - 0.92 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	1.417 B 552.1	A
45		4-(6-((6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)sulfonyl)pyridin-3-yl)-N-cyclopropylbenzamide	^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.11 (s, 1H), 8.59 (d, *J*=4.0 Hz, 1H), 8.51 (d, *J*=8.1 Hz, 1H), 8.27 (d, *J*=8.2 Hz, 1H), 8.03 - 7.87 (m, 4H), 7.38 (t, *J*=8.2 Hz, 1H), 6.75 (d, *J*=8.3 Hz, 2H), 3.74 (s, 6H), 2.88 (dd, *J*=7.2, 3.4 Hz, 1H), 2.19 - 2.00 (m, 2H), 1.36 - 1.22 (m, 2H), 1.14 - 1.01 (m, 2H), 0.78 - 0.67 (m, 2H), 0.67 - 0.49 (m, 5H)	1.861 D 604.4	A
46		6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxy-3-(pyridin-2-ylsulfonyl)pyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.73 (d, *J*=4.0 Hz, 1H), 8.19 (br. s., 2H), 7.74 (br. s., 1H), 7.37 (t, *J*=8.2 Hz, 1H), 6.74 (d, *J*=8.4 Hz, 2H), 3.73 (s, 4H), 2.55 (s, 2H), 2.10 (t, *J*=7.6 Hz, 2H), 1.36 - 1.20 (m, 2H), 1.14 - 0.95 (m, 2H), 0.62 (t, *J*=7.2 Hz, 3H)	1.256 B 445.3	A
47		3-((5-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyridin-2-yl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.56 (br. m., 2H), 7.66 (br. m., 1H), 7.28 (m, 4H), 6.78 - 6.58 (m, 3H), 3.68 (br. s., 6H), 1.42 - 1.19 (m, 2H), 1.15 (t, *J*=7.2 Hz, 2H), 1.03 (d, *J*=5.6 Hz, 2H), 0.69 - 0.48 (m, 3H)	1.344 B 561.2	A

48		3-((4H-1,2,4-triazol-3-yl)sulfonyl)-6-butyl-5-(2,6-dimethoxyphenyl)-4-hydroxypyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.35 (br. s., 1H), 7.23 (t, *J*=8.3 Hz, 1H), 6.63 (d, *J*=8.4 Hz, 2H), 2.55 (s, 6H), 2.01 - 1.85 (m, 3H), 1.28 (quin, *J*=7.6 Hz, 2H), 1.12 - 0.97 (m, 2H), 0.63 (t, *J*=7.3 Hz, 3H)	0.970 B 435.1	B

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring A is independently selected from -$(CH_2)_{0-1}$-5- or 6-membered aryl and heterocyclyl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^{3a}, O, and S, each substituted with 1-3 R^3 and 1-2 R^5 ; provided R^3 and R^5 are not both H;

ring B is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, aryl, bicyclic carbocyclyl, 6-membered heteroaryl, bicyclic heterocyclyl, each substituted with 1-3 R^1;

R^1 is independently selected from H, F, Cl, Br, NO_2, -$(CH_2)_nOR^b$, $(CH_2)_nS(O)_pR_c$, -$(CH_2)_nC(=O)R^b$, -$(CH_2)_nNR^aR^a$, -$(CH_2)_nCN$, -$(CH_2)_nC(=O)NR^aR^a$, -$(CH_2)_nNR^aC(=O)R^b$, -$(CH_2)_nNR^aC(=O)NR^aR^a$, -$(CH_2)_nNR^aC(=O)OR^b$, -$(CH_2)_nOC(=O)NR^aR^a$, -$(CH_2)_nC(=O)OR^b$, -$(CH_2)_nS(O)_pNR^aR^a$, -$(CH_2)_nNR^aS(O)_pNR^aR^a$, -$(CH_2)_nNR^aS(O)_pR^c$, C_{1-4} alkyl substituted with 0-3 R^e, -$(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl substituted with 0-3 R^e, aryl substituted with 0-3 R^e, heterocyclyl substituted with 0-3 R^e, and C_{3-6} cycloalkyl substituted with 0-3 R^e; provided when R^2 is C_{1-5} alkyl, the carbon atom except the one attached to the pyridine ring may be replaced by O, N, and S;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, -$(CH_2)_nOR^b$, -$(CH_2)_nNR^aR^a$, -$(CH_2)_nCN$, -$(CH_2)_nC(=O)R^b$, -$(CH_2)_nC(=O)OR^b$, -$(CH_2)_nC(=O)NR^aR^a$, -$(CH_2)_nNHC(=O)R^b$, -$(CH_2)_nNHC(=O)NR^aR^a$, -$(CH_2)_nNHC(=O)OR^b$, -$(CH_2)_nNHS(O)_pNR^aR^a$,

$-(CH_2)_nNHS(O)_pR^c$ $-(CH_2)_nS(O)_pR_c$, $-(CH_2)_nS(O)_pNR^aR^a$, and $-(CH_2)_nOC(=O)NR^aR^a$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-S(O)_pR_c$, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, $S(O)_pNR^aR^a$, R^6, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, R^6, $-OR^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, $-OC(=O)NR^aR^6$, $-S(O)_pNR^aR^6$, $-NR^aS(O)_pNR^aR^6$, and $-NR^aS(O)_pR^6$;

R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-6 R^8;

R^7 is independently selected from H, C_{1-4} alkyl, and $(CH_2)_n$-C_{3-12} carbocyclyl substituted with 0-3 R^e;

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_nCN$, $-(CH_2)_nOR^b$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nC(=O)NR^aR^a$, $-(CH_2)_nNR^aR^a$, $-(CH_2)_nNR^aC(=O)R^b$, $-(CH_2)_nNR^aC(=O)OR^b$, $-(CH_2)_nNR^aC(=O)NR^aR^a$, $-(CH_2)_nOC(=O)NR^aR^a$, $-(CH_2)_nS(O)_pR_c$, $-(CH_2)_nS(O)_pNR^aR^a$, $-(CH_2)_nNR^aS(O)_pNR^aR^a$, $-(CH_2)_nNR^aS(O)_pR^c$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

R^c is independently selected from C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6}alkenyl substituted with 0-5 R^e, C_{2-6}alkynyl substituted with 0-5 R^e, C_{3-6}carbocyclyl, and heterocyclyl;

R^d is independently selected from H and C_{1-4}alkyl substituted with 0-5 R^e;

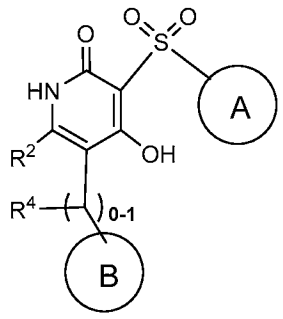
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl, or R^f and R^f together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with C_{1-4}alkyl;

n is independently selected from zero, 1, 2, 3, and 4; and

p is independently selected from zero, 1, and 2.

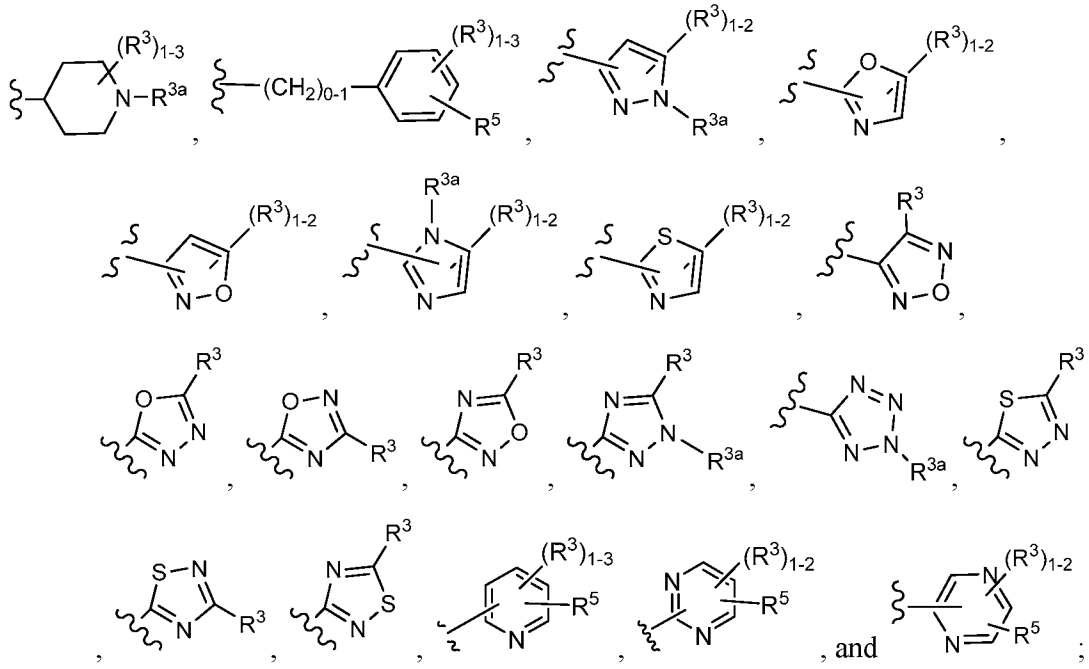
2. The compound of claim 1, having Formula (II):



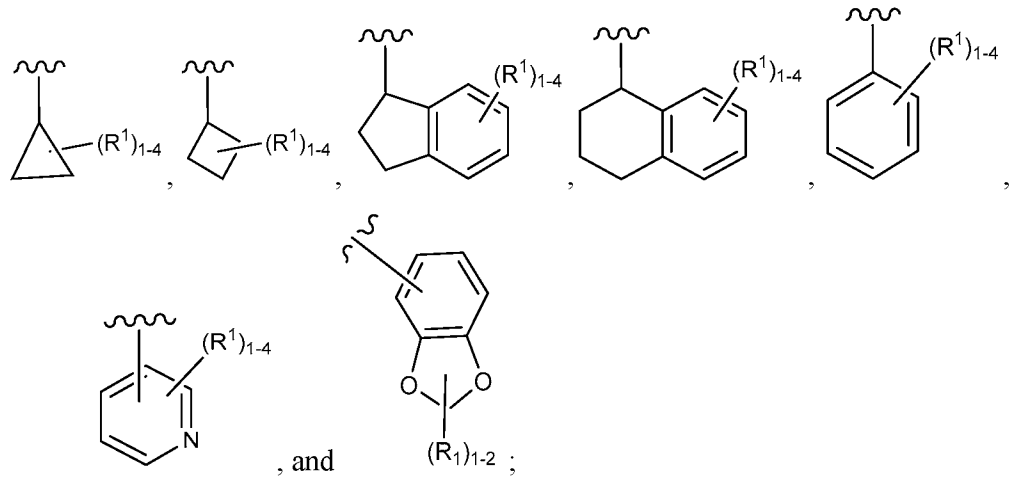
(II)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring A is independently selected from



ring B is independently selected from



R^1 is independently selected from H, F, Cl, Br , $-OR^b$, CN, C_{1-4} alkyl substituted with 0-3 R^e and C_{3-6} cycloalkyl substituted with 0-3 R^e;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, heterocyclyl substituted with 0-3 R^e, and C_{3-6} cycloalkyl; provided when R^2 is C_{1-5} alkyl, the carbon atom except the one attached to the pyridine ring may be replaced by O, N, and S;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl; $-OR^b$, $-NR^aR^a$, -CN, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$,

-NHC(=O)R^b, -NHC(=O)NR^aR^a, -NHC(=O)OR^b, -NHS(O)$_pR^c$ -S(O)$_pR_c$, -S(O)$_pNR^aR^a$, and -OC(=O)NR^aR^a;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, -C(=O)R^b, -C(=O)NR^aR^a, -C(=O)OR^b, R^6, -S(O)$_pR^6$, -C(=O)R^6, -C(=O)NR^aR^6, -C(=O)OR^6, and -S(O)$_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, -$(CH_2)_n$-C_{3-6} cycloalkyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, R^6, -OR^6, -S(O)$_pR^6$, -C(=O)R^6, -C(=O)OR^6, -NR^aR^6, -C(=O)NR^aR^6, -$NR^aC(=O)R^6$, -$NR^aC(=O)OR^6$, -OC(=O)NR^aR^6, -S(O)$_pNR^aR^6$, -$NR^aS(O)_pNR^aR^6$, and -$NR^aS(O)_pR^6$;

R^6 is independently selected from -$(CR^7R^7)_n$-aryl, -$(CR^7R^7)_n$-C_{3-6} cycloalkyl, and -$(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

R^7 is independently selected from H and C_{1-4} alkyl;

R^8 is independently selected from H, F, Cl, Br, -OR^b, -$(CH_2)_n$C(=O)R^b, -$(CH_2)_n$C(=O)OR^b, -$(CH_2)_n$$NR^aR^a$, CN, -$(CH_2)_n$C(=O)$NR^aR^a$, -NHC(=O)$OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e-$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

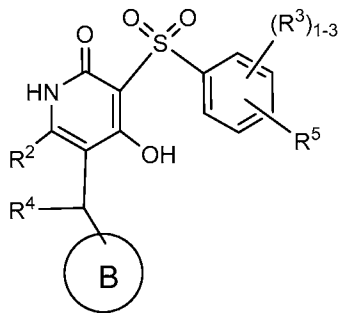
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, -$(CH_2)_n$$OR_f$, S(O)$_pR^f$, C(=O)$NR^fR^f$, $NR^fC(=O)R^f$, S(O)$_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, OC(=O)NR^fR^f and -$(CH_2)_n$$NR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

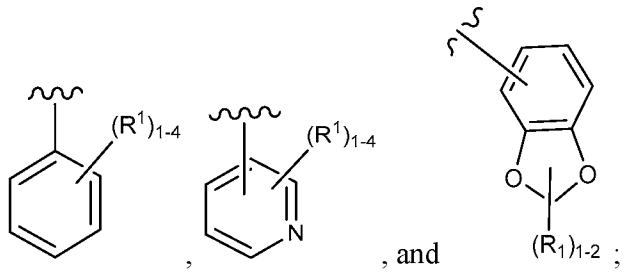
3. The compound of claim 2, having Formula (III):



(III)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring B is independently selected from



, , and ;

R^1 is independently selected from H, F, Cl, CN, and OC_{1-4} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, and Br;

R^4 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl, C_{3-6} cycloalkyl substituted with 0-3 R^e, and heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected H and R^6;

R^6 is independently selected from aryl, C_{3-6} cycloalkyl, and heteroaryl, each substituted with 1-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

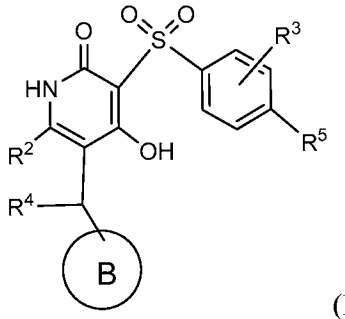
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

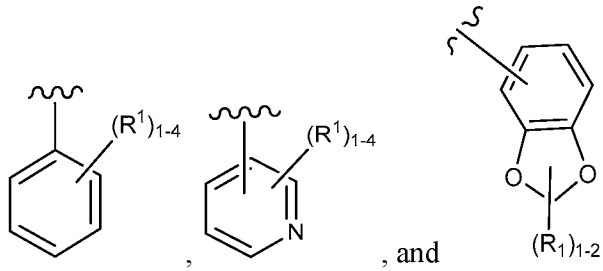
4. The compound of claim 3, having formula (IV):



(IV)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

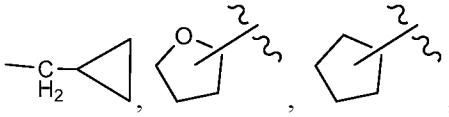
ring B is independently selected from



, , and ;

R^1 is independently selected from H, F, Cl, CN, and OMe;

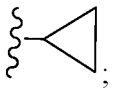
R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,



, , , $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

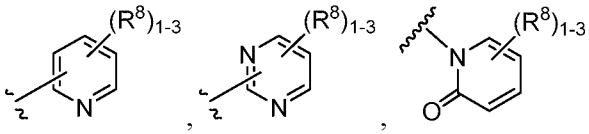
R^3 is independently selected from H, F, Cl, and Br;

R^4 is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH{=}CH_2$, and

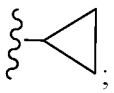


;

R^5 is R^6;

R^6 is independently selected from 

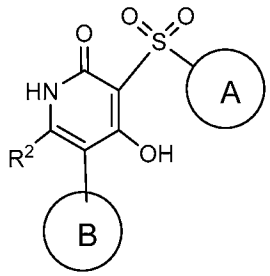
, , , and



; and

R^8 is independently selected from H, F, Cl, Br, $-OCH_3$, and C_{1-4} alkyl.

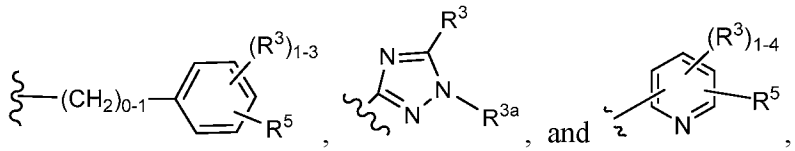
5. The compound of claim 2, having Formula (V):



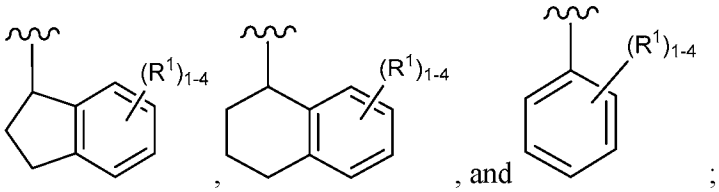
(V)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring A is independently selected from



ring B is independently selected from



R^1 is independently selected from H, F, Cl, CN, and OC_{1-4} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $-OR^b$, $-NR^aR^a$, -CN, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-NHC(=O)R^b$, and $-NHC(=O)OR^b$;

R^4 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl, C_{3-6} cycloalkyl substituted with 0-3 R^e, and heterocyclyl substituted with 0-3 R^e;

R^5 is independently selected from H, aryl R^6, $-OR^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, $-OC(=O)NR^aR^6$, $-S(O)_pNR^aR^6$, $-NR^aS(O)_pNR^aR^6$, and $-NR^aS(O)_pR^6$;

R^6 is independently selected from aryl, C_{3-6} cycloalkyl, and heteroaryl, each substituted with 1-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{2-6} alkenyl substituted with 0-5 R^e, C_{2-6} alkynyl substituted with 0-5 R^e, $-(CH_2)_n-C_{3-10}$carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e;

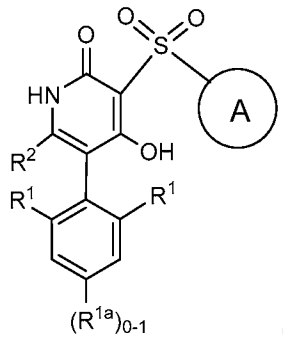
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R_f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR_f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ and $-(CH_2)_nNR^fR^f$;

R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

n is independently selected from zero, 1, 2, and 3; and

p is independently selected from zero, 1, and 2.

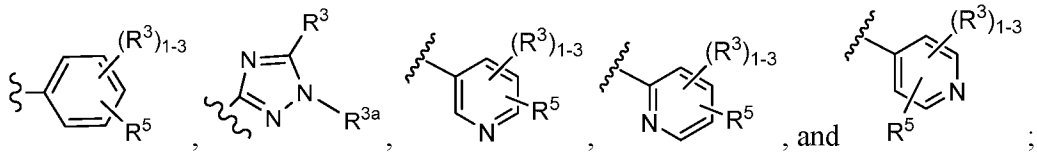
6. The compound according to claim 5 having Formula (VI):



(VI)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring A is independently selected from



;

R^1 is independently selected from F, Cl, OH, and OC_{1-4} alkyl;

R^{1a} is independently selected from F, Cl, and C_{1-2} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl and $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, Br, C_{1-5} alkyl substituted with 0-3 R^e, C_{1-5} alkyl $-OR^b$, $-NR^aR^a$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-NHC(=O)R^b$, $-NHC(=O)OR^b$, and $-NHC(=O)NHR^a$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, $-R^6$, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^4 is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, C_{2-5} alkenyl substituted with 0-3 R^e, $-(CH_2)_n$-C_{3-6} cycloalkyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

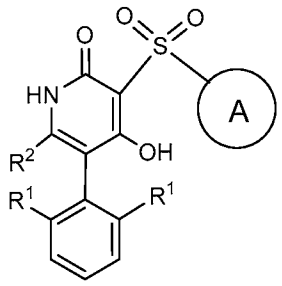
R^5 is independently selected from H, R^6, $-OR^6$, $-C(=O)R^6$, $-C(=O)OR^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, $-NR^aC(=O)R^6$, $-NR^aC(=O)OR^6$, and $-OC(=O)NR^aR^6$;

R^6 is independently selected from $-(CH_2)_n$-aryl, $-(CH_2)_n$-C_{3-6} cycloalkyl, and $-(CH_2)_n$-heteroaryl, each substituted with 0-3 R^8;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e; and

n is independently selected from zero, 1, 2, and 3.

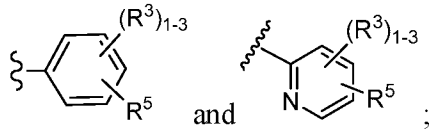
7. The compound according to claim 6, having Formula (VII):



(VII)

or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

ring A is independently selected from



;

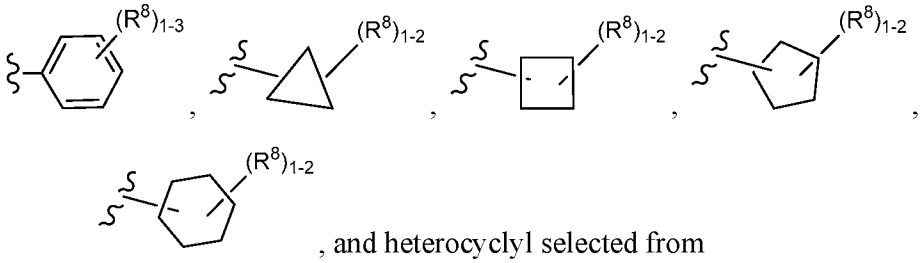
R^1 is -OC_{1-4} alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, -$(CH_2)_{1-4}OC_{1-5}$alkyl, and -$(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

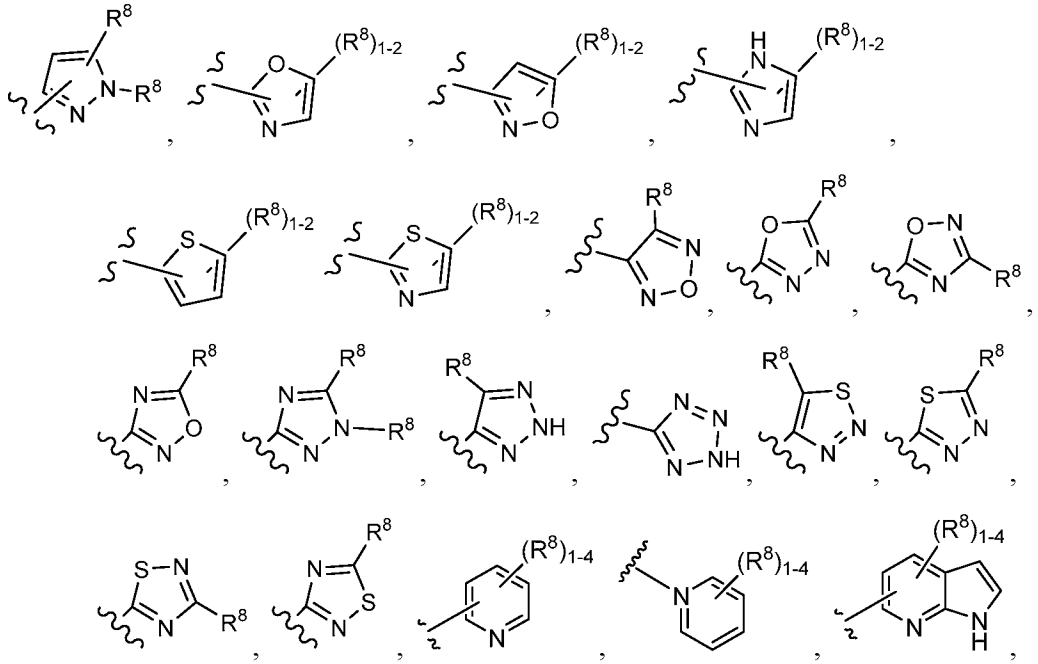
R^3 is independently selected from H, F, Cl, Br, C_{1-4} alkyl, C_{2-4} alkenyl, -NHR^a, -$C(=O)OR^a$, -$C(=O)NHR^a$, -$NHC(=O)R^b$, -$NHC(=O)OR^b$, and -$NHC(=O)NHR^a$;

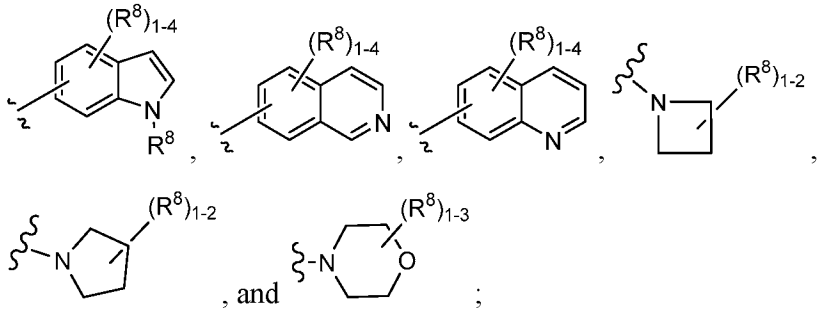
R^5 is independently selected from H, R^6, -$C(=O)R^6$, -NR^aR^6, -$C(=O)NR^aR^6$, and -$NHC(=O)R^6$

R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from





; and

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

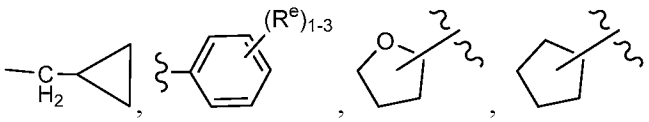
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

8. The compound according to claim 7, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-OC_{1-4}$ alkyl;

R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,

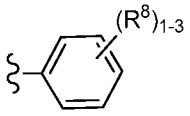
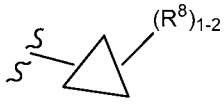


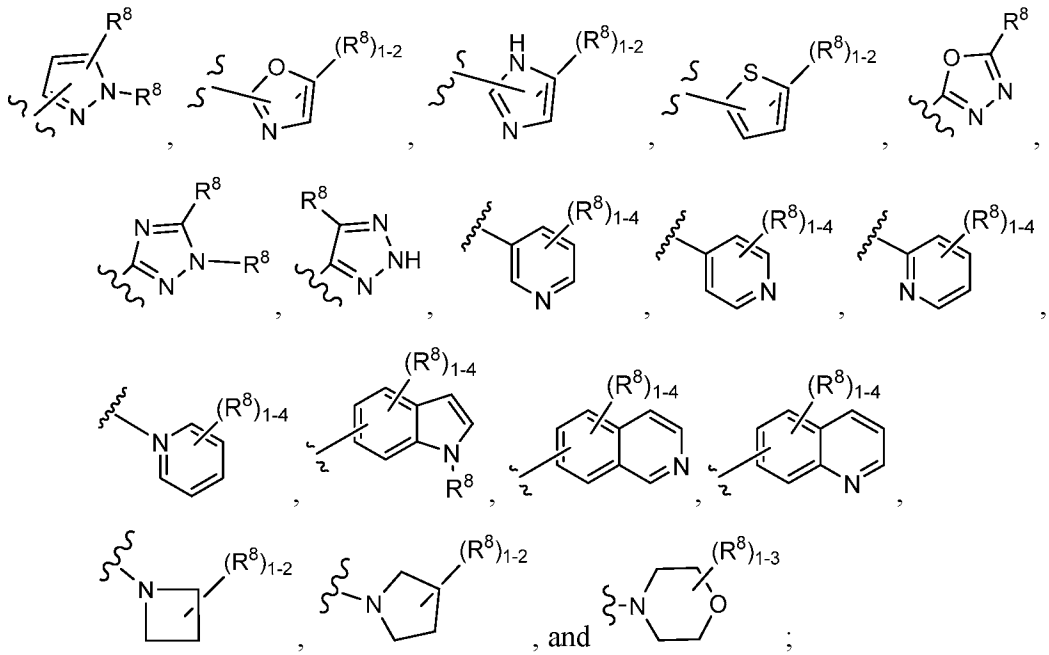
$-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

R^3 is independently selected from H, F, Cl, Br, $-C(=CH_2)CH_3$, $-C(=O)OR^b$, $-C(=O)NHR^a$, $-NHC(=O)OR^b$, and $-NHC(=O)NHR^a$;

R^5 is independently selected from R^6, -C(=O)R^6, -N$R^a$$R^6$, -C(=O)N$HR^6$, and -NHC(O)$R^6$;

R^6 is independently selected from carbocyclyl selected from


and

, and heterocyclyl selected from



R^8 is independently selected from H, F, Cl, Br, --$(CH_2)_nOR^b$, -C(=O)R^b, -C(=O)OR^b, -$(CH_2)_nNR^aR^a$, CN, -C(=O)NR^aR^a, -NHC(=O)R^b, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

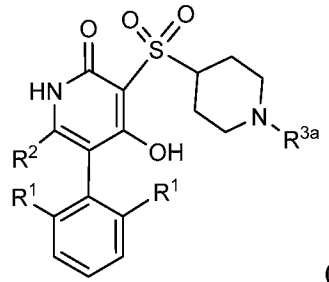
R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

9. The compound according to claim 6 having Formula (VIII):



(VIII)

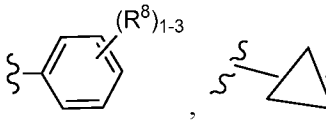
or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

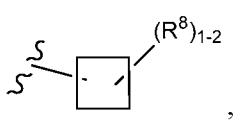
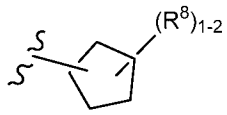
R^1 is $-OC_{1-4}$ alkyl;

R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

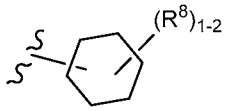
R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-S(O)_pR_c$, $-C(=O)R^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^b$, $S(O)_pNR^aR^a$, R^6, $-S(O)_pR^6$, $-C(=O)R^6$, $-C(=O)NR^aR^6$, $-C(=O)OR^6$, and $-S(O)_pNR^aR^6$;

R^6 is independently selected from carbocyclyl selected from

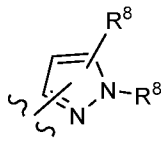
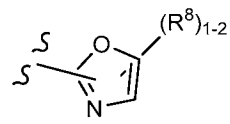
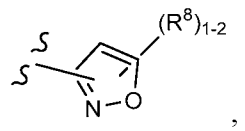
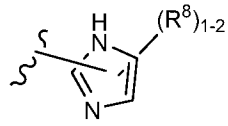


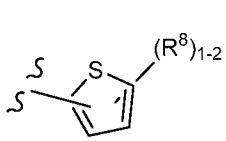
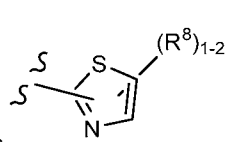
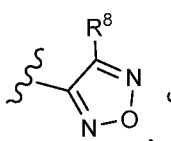
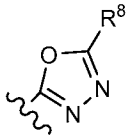
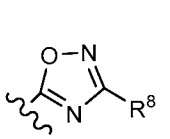



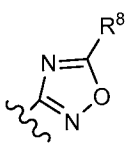
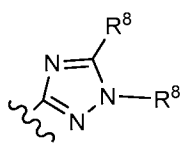
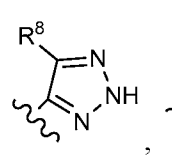
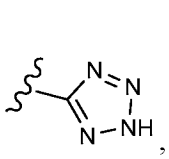
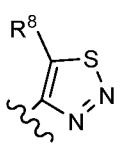
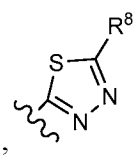
, and

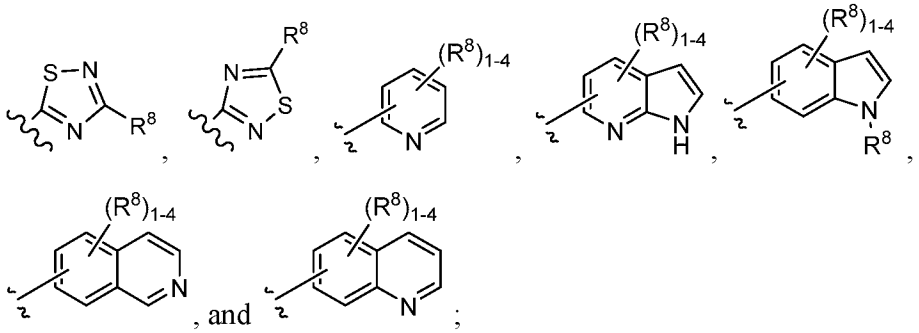


, and heterocyclyl selected from



R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

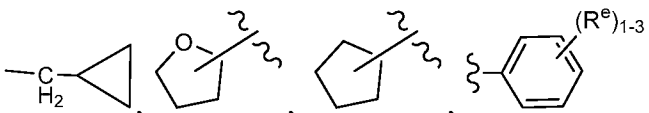
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

10. The compound according to claim 9, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-OC_{1-4}$ alkyl;

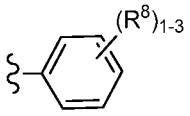
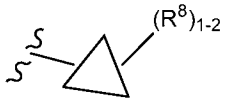
R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,



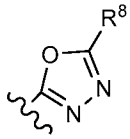
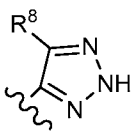
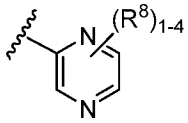
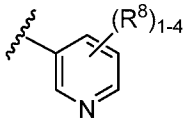
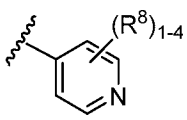
$-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

R^{3a} is independently selected from H, C_{1-5} alkyl substituted with 0-3 R^e, $-C(=O)R^b$, $-C(=O)OR^b$, $-(CH_2)_n$-R^6, and $-C(=O)R^6$;

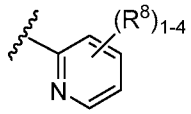
R^6 is independently selected from carbocyclyl selected from

and , and heterocyclyl selected from

, and



;

R^8 is independently selected from H, F, Cl, Br, --$(CH_2)_nOR^b$, -C(=O)R^b, -C(=O)OR^b, -$(CH_2)_nNR^aR^a$, CN, -C(=O)NR^aR^a, -NHC(=O)R^b, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

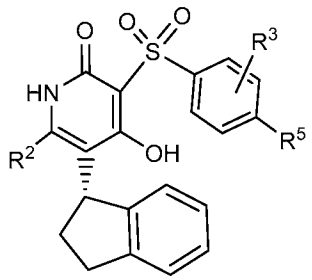
R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, -$(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H and C_{1-6} alkyl substituted with 0-5 R^e;

R^e is independently selected from OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

11. The compound according to claim 5 having Formula (IX):



(IX)

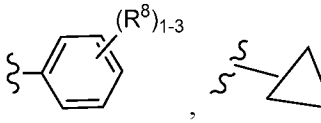
or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

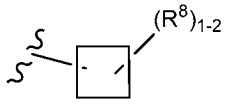
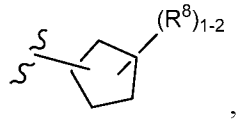
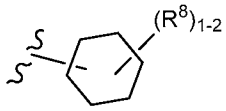
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, heteroaryl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^3 is independently selected from H, F, Cl, and Br;

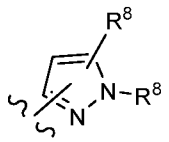
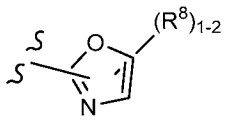
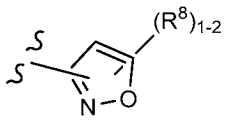
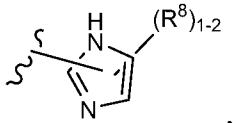
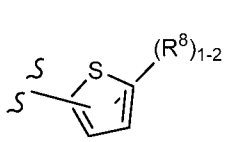
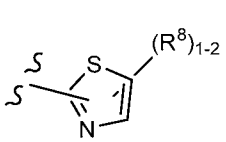
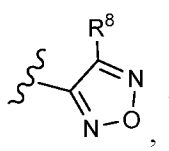
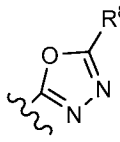
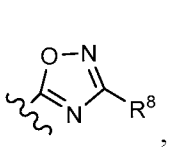
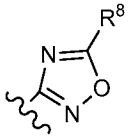
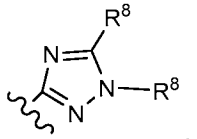
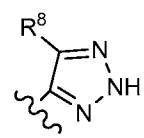
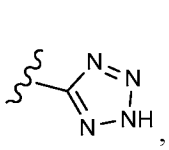
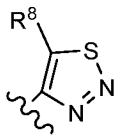
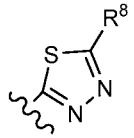
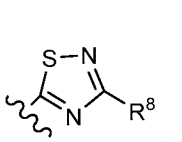
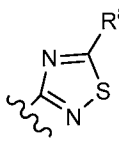
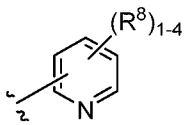
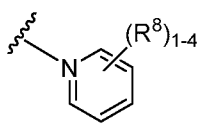
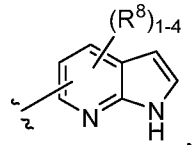
R^5 is independently selected from H, R^6, $-C(=O)R^6$, and $-C(=O)NR^aR^6$;

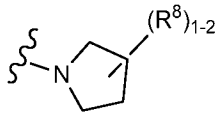
R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from

, and , and ;

R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n$-C_{3-10}carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R^e;

R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

n is independently selected from zero, 1, 2, and 3.

12. A compound according any one of claims 1-11, wherein the compound is selected from the exemplified examples or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1-11, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

14. A method of treating cardiovascular diseases, comprising administering to a patient in need there of a therapeutically effective amount of the pharmaceutical composition of claim 13.

15. The method of claim 14 wherein said cardiovascular diseases are coronary heart disease, stroke, heart failure, systolic heart failure, diastolic heart failure, diabetic heart failure, heart failure with preserved ejection fraction, cardiomyopathy, myocardial infarction, left ventricular dysfunction, left ventricular dysfunction after myocardial

infarction, cardiac hypertrophy, myocardial remodeling, myocardial remodeling after infarction or after cardiac surgery and valvular heart diseases.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/037370

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/71 C07D213/74 C07D213/89 C07D401/12 C07D471/04
A61K31/444 A61P9/10
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2016/196771 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 8 December 2016 (2016-12-08) claim 1	1-15
A	CAO JIANGANG ET AL: "Targeting Drugs to APJ Receptor: The Prospect of Treatment of Hypertension and Other Cardiovascular Diseases", CURRENT DRUG TAR, BENTHAM SCIENCE PUBLISHER, US, vol. 16, no. 2, 1 February 2015 (2015-02-01), pages 148-155, XP009191040, ISSN: 1389-4501 page 152, left-hand column - right-hand column; figure 3	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2017	24/07/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Johnson, Claire

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/037370

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016196771 A1	08-12-2016	TW 201708214 A	01-03-2017
		US 2016355507 A1	08-12-2016
		UY 36705 A	30-11-2016
		WO 2016196771 A1	08-12-2016