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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2018 (19.04.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/071622 A1

(51) International Patent Classification:
C07D 213/74 (2006.01) *C07D 413/04* (2006.01)
C07D 401/06 (2006.01) *C07D 417/04* (2006.01)
C07D 401/14 (2006.01) *C07D 417/14* (2006.01)
C07D 413/14 (2006.01) *A61K 31/4427* (2006.01)
C07D 401/04 (2006.01) *A61P 9/00* (2006.01)

(21) International Application Number:
PCT/US2017/056265

(22) International Filing Date:
12 October 2017 (12.10.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/408,272 14 October 2016 (14.10.2016) US

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(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.

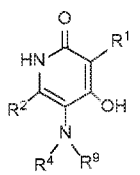
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

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

WO 2018/071622 A1

(54) Title: 3-SULFONYL-5-AMINOPYRIDINE-2,4-DIOL APJ AGONISTS



(I)

(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.

3-SULFONYL-5-AMINOPYRIDINE-2,4-DIOL APJ 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. 62/408272, filed October 14, 2016, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention provides novel 3-sulfonyl-5-aminopyridine-2,4-diol 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 3-sulfonyl-5-aminopyridine-2,4-diol 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.

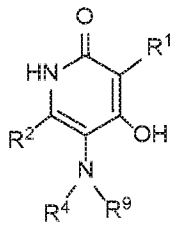
The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

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

DETAILED DESCRIPTION OF THE INVENTION

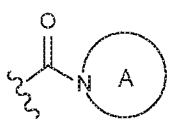
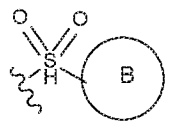
I. COMPOUNDS OF THE INVENTION

In a first aspect, the present invention provides, *inter alia*, compounds of Formula (I):

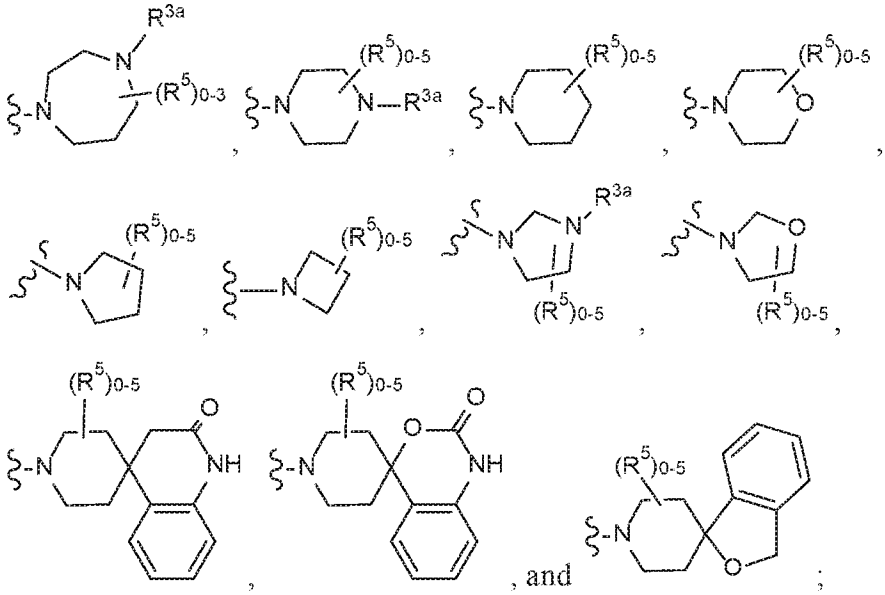


(I)

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

R^1 is independently selected from  and  ;

Ring A is independently selected from



Ring B is independently selected from 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;

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, $-(CH_2)_nOR^b$, $-(CH_2)_nNR^aR^a$, $-(CH_2)_nCN$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nC(=O)NR^aR^a$, $-(CH_2)_nNHC(=O)R^b$, $-(CH_2)_nNHC(=O)NR^aR^a$, $-(CH_2)_nNHC(=O)OR^b$, $-(CH_2)_nNHS(O)_pNR^aR^a$, $-(CH_2)_nNHS(O)_pR^c$ $-(CH_2)_nS(O)_pR_c$, $-(CH_2)_nS(O)_pNR^aR^a$, $-(CH_2)_nOC(=O)NR^aR^a$;

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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, aryl, bicyclic carbocyclyl, 6-membered heteroaryl, bicyclic heterocyclyl, each substituted with 1-6 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a mono or bicyclic heterocyclic ring substituted with 1-6 R^{10};

R^{10} 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^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;

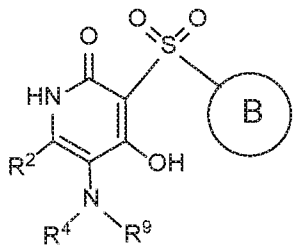
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$,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

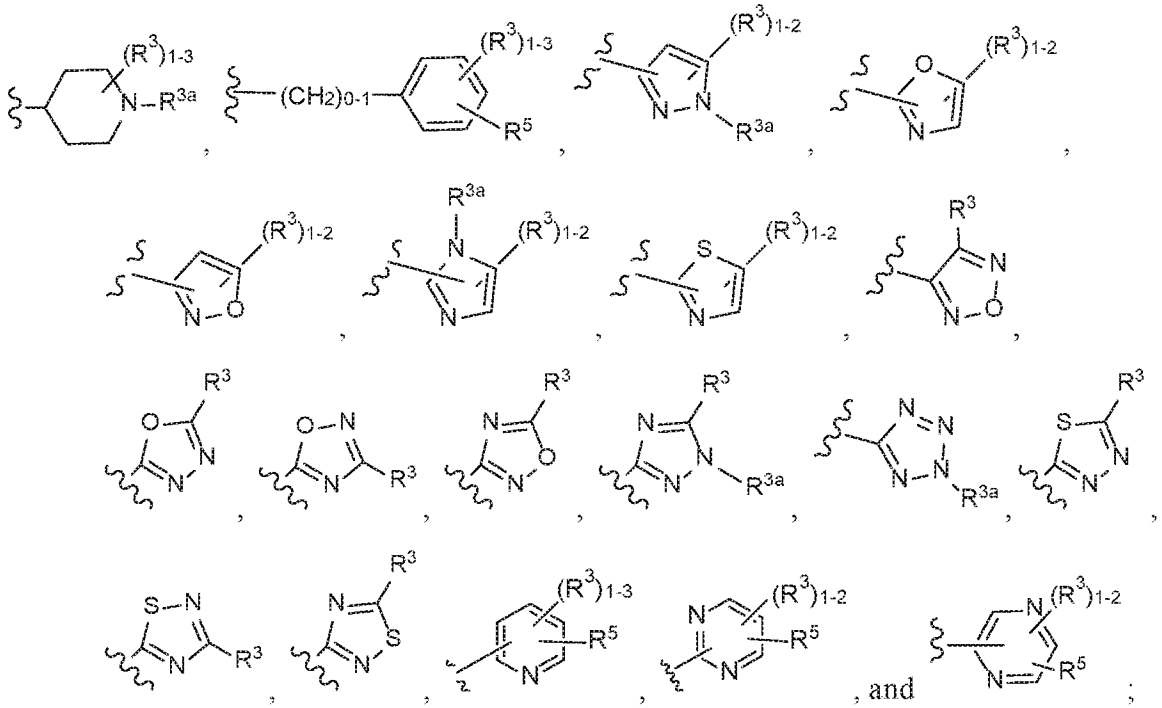
In a second aspect, the present invention provides compounds of Formula (II):



(II)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect, wherein

Ring B is independently selected from



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

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 and C_{1-5} alkyl 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 $-NR^aS(O)_pR^6$;

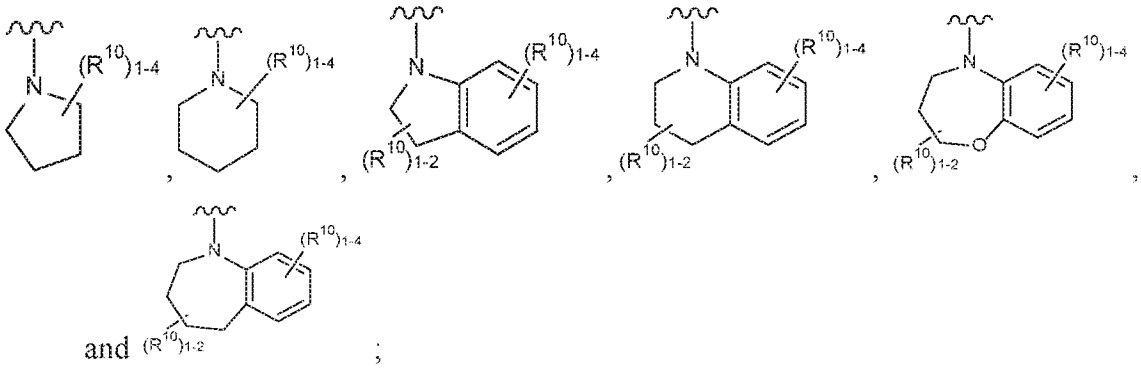
R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

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

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_nOR^b$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nNR^aR^a$, 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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, and aryl, each substituted with 1-6 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



and ;

R^{10} 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^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;

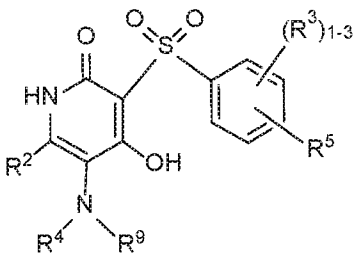
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ 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 a third aspect, the present invention provides compounds of Formula (III):



(III)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first or second aspect, wherein

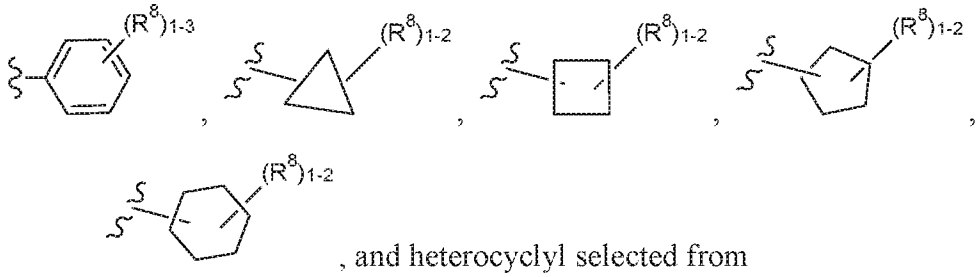
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

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

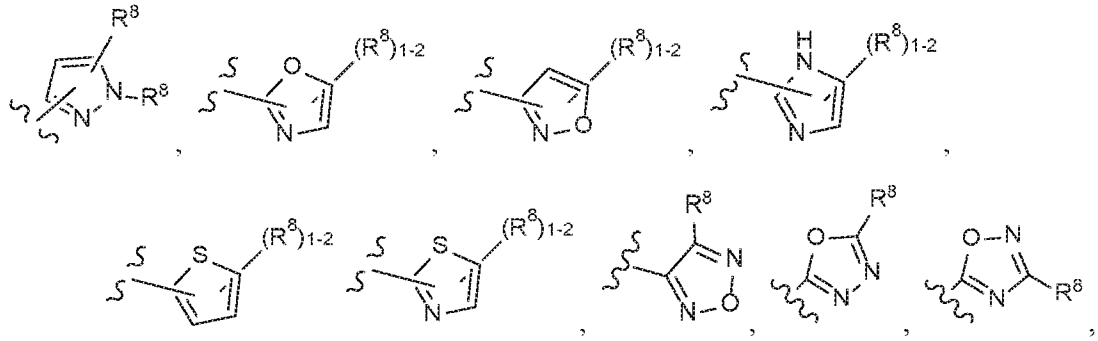
R^4 is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

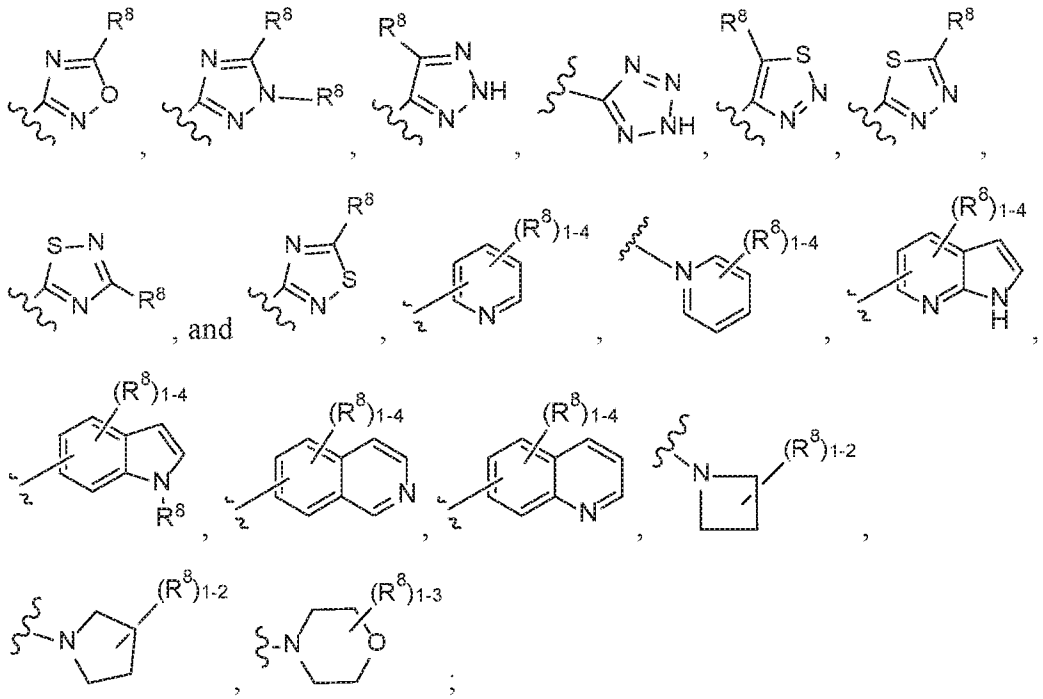
R^5 is independently selected from H, R^6, $-C(=O)R^6$, $-NR^aR^6$, $-C(=O)NR^aR^6$, and $-NHC(=O)R^6$;

R^6 is independently selected from carbocyclyl selected from



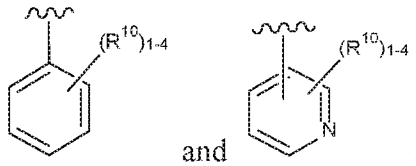
, and heterocyclyl selected from





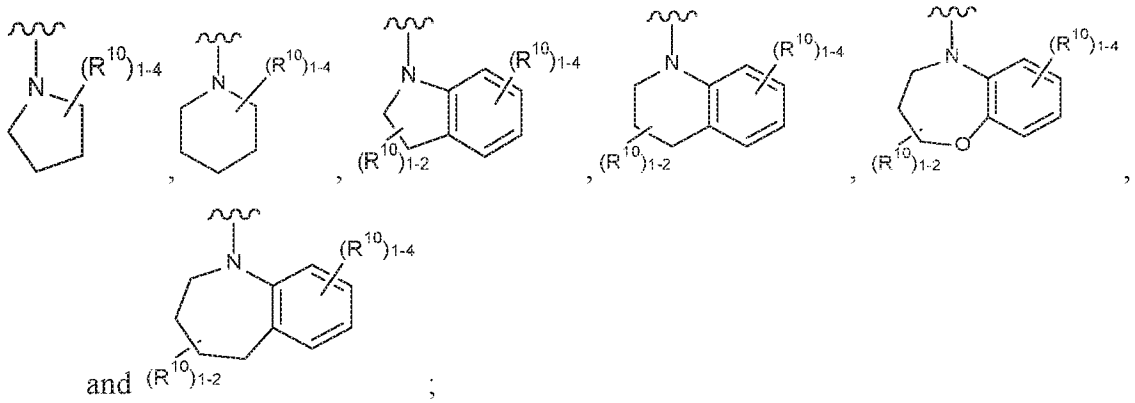
R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_nOR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $-(CH_2)_n-C_{3-6}$ carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^9 is independently selected from



;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

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;

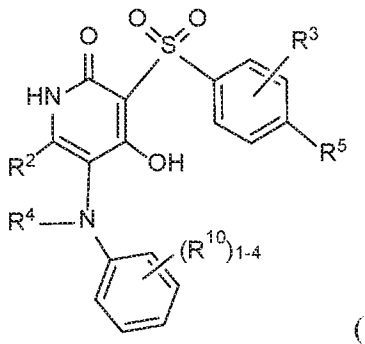
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$,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

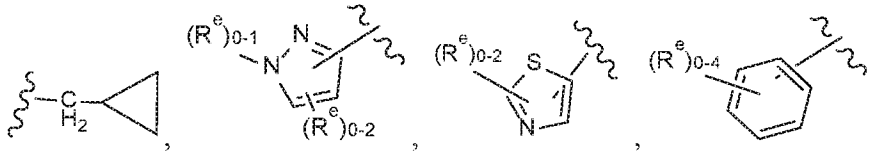
In a fourth aspect, the present invention provides compounds of Formula (IV):



(IV)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of any of the first, second and third aspects, wherein

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

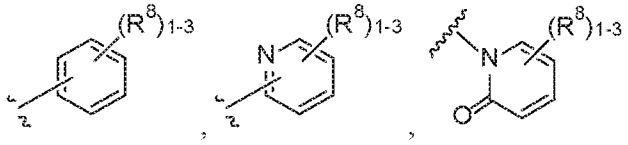
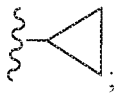


, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

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

R^4 is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH_2(CH_3)_2$;

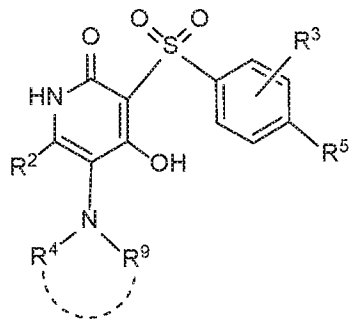
R^5 is R^6;

R^6 is independently selected from  , and  ;

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl and $-C(=O)N(C_{1-4}alkyl)_2$; and

R^{10} is independently selected from H, F, Cl, CN, $-CH_3$, $-CH_2CH_3$, and -OMe.

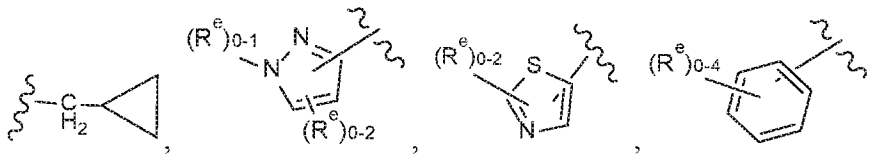
In a fifth aspect, the present invention provides compounds of Formula (V):



(V)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of any of the first, second and third aspects, wherein

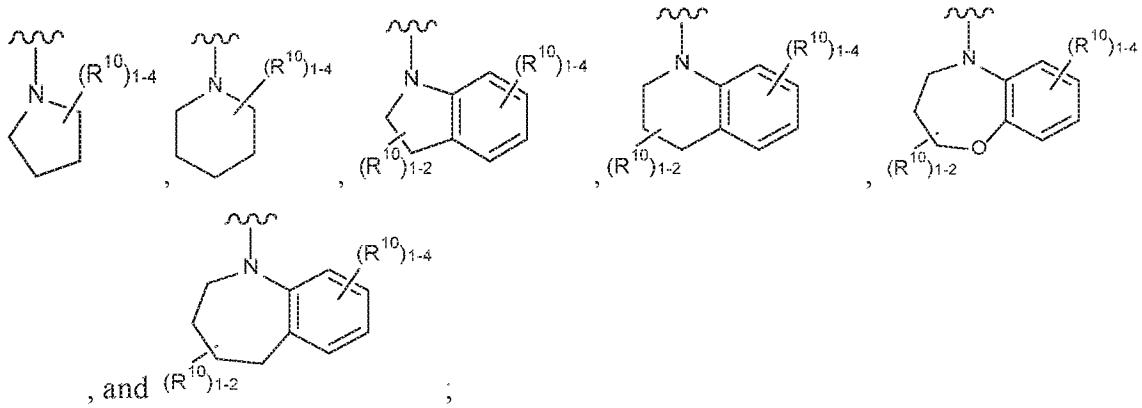
R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,



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

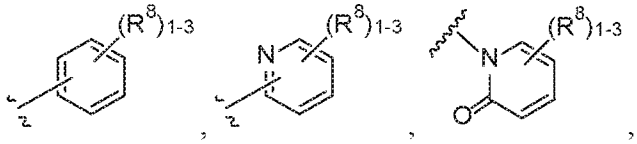
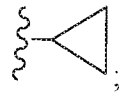
R^3 is independently selected from H, F, Cl, and Br;

R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



, and ;

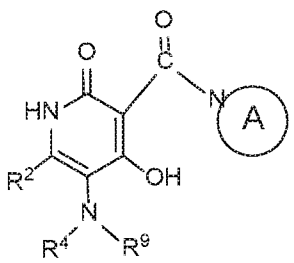
R^5 is R^6;

R^6 is independently selected from  , and  ;

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl and $-C(=O)N(C_{1-4}alkyl)_2$; and

R^{10} is independently selected from H, F, Cl, CN, $-CH_3$, $-CH_2CH_3$, and $-OCH_3$.

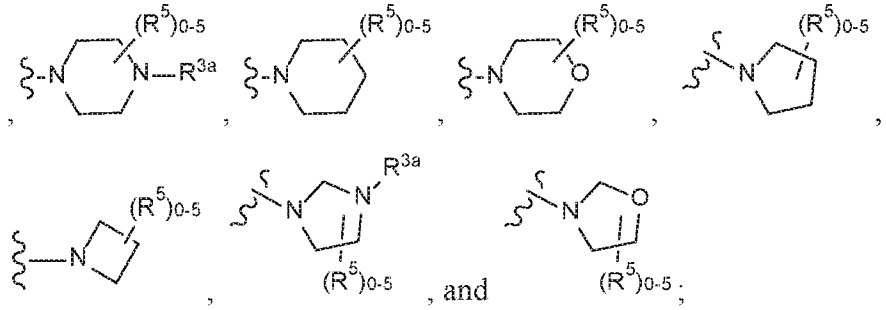
In a sixth aspect, the present invention provides compounds of Formula (VI):



(VI)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first aspect, wherein

Ring A is independently selected from



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^{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 and C_{1-5} alkyl 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 $-NR^aS(O)_pR^6$;

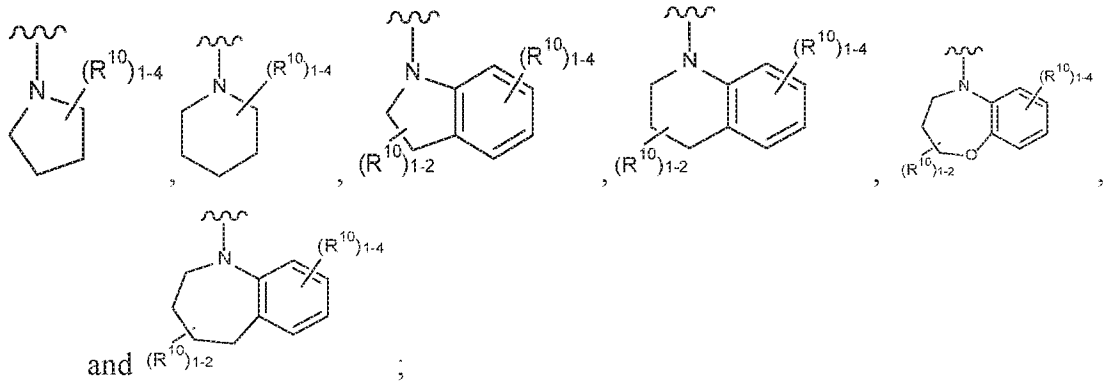
R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, and aryl, each substituted with 1-3 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



;

R^{10} 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^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;

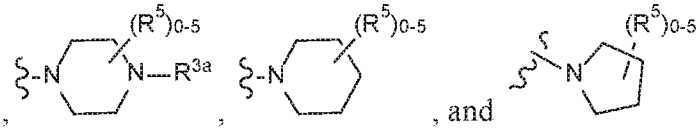
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, -$(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ 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 a seventh aspect, the present invention provides compounds of Formula (VI), or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first and sixth aspects, wherein Ring A is independently selected from



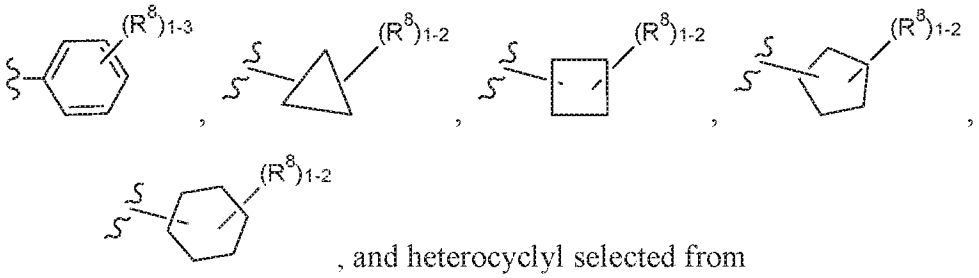
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^{3a} is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

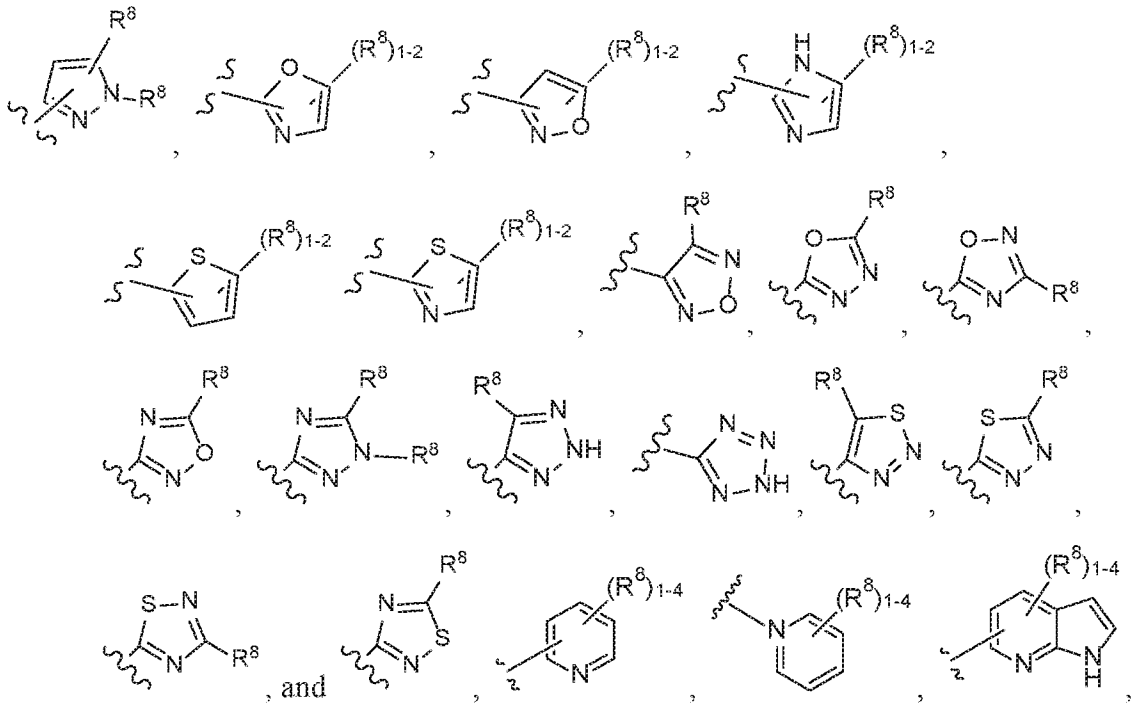
R^4 is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

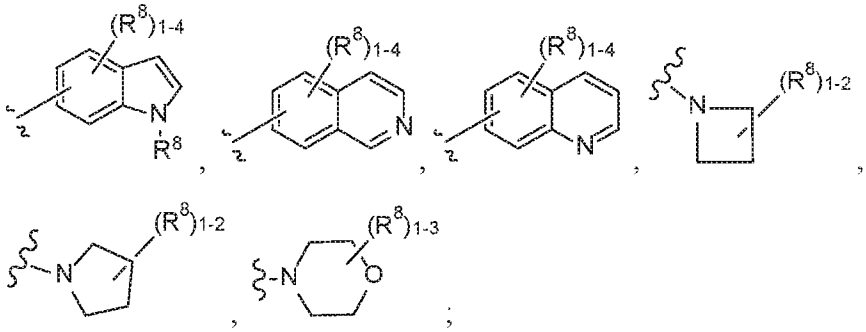
R^5 is independently selected H and R^6;

R^6 is independently selected from carbocyclyl selected from



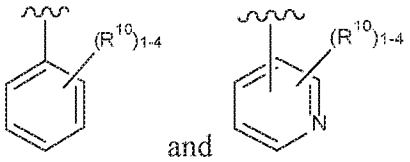
, and heterocyclyl selected from





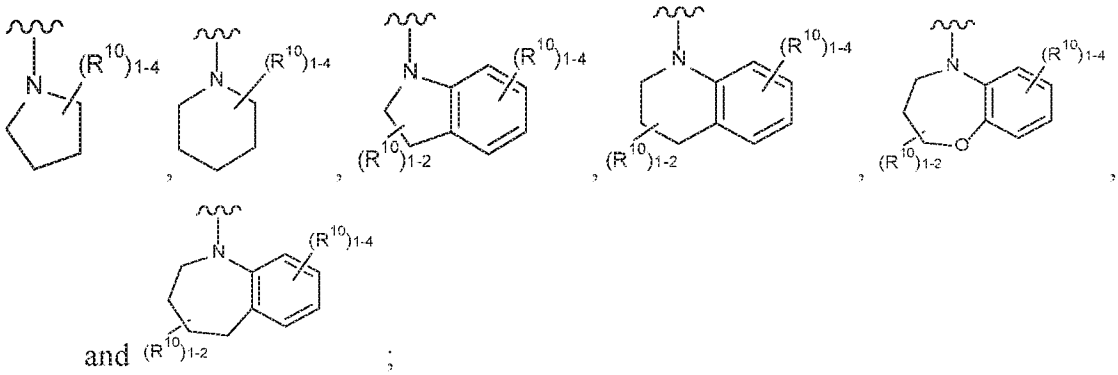
R^8 is independently selected from H, F, Cl, Br, $-OR^b$, $-C(=O)R^b$, $-C(=O)OR^b$, $-NR^aR^a$, CN, $-C(=O)NR^aR^a$, $-NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, $-(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^9 is independently selected from



;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

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;

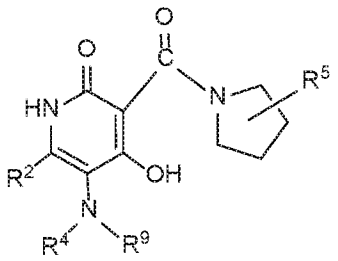
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$, $S(O)_pNR^fR^f$, $NR^fS(O)_pR^f$, $NR^fC(=O)OR^f$, $OC(=O)NR^fR^f$ 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 an eighth aspect, the present invention provides compounds of Formula (VII):



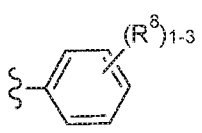
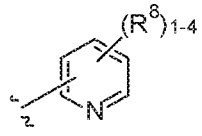
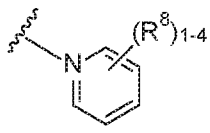
(VII)

or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first, sixth, and seventh aspects, 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, 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;

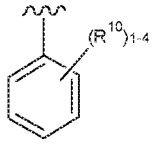
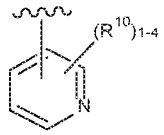
R^4 is independently selected from H and C_{1-4} alkyl;

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

R^6 is independently selected from  ,  , and  ;

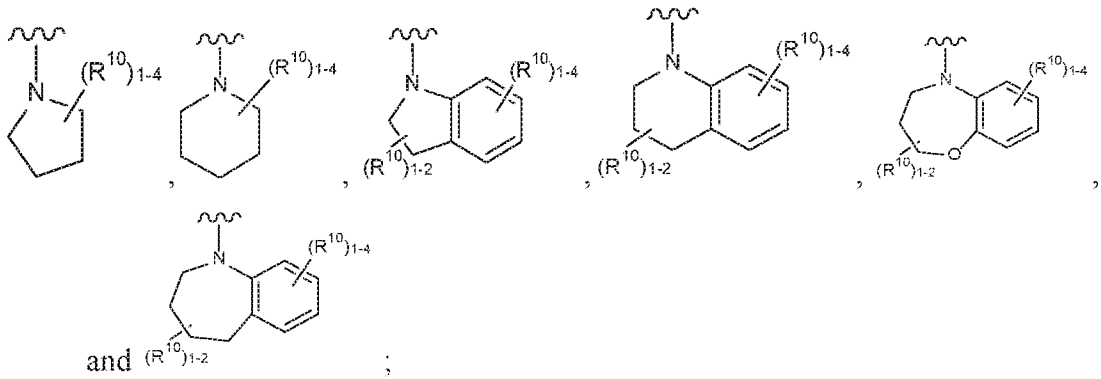
R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl, and $-C(=O)N(C_{1-4}alkyl)_2$;

R^9 is independently selected from

and ;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



and ;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

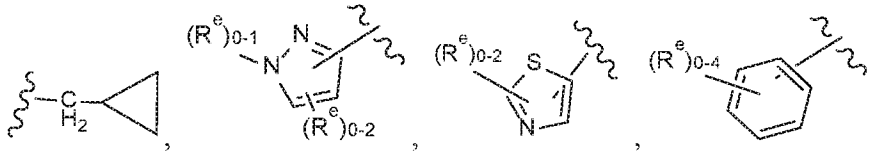
R^a is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, $-(CH_2)_n-C_{3-10}$carbocyclyl substituted with 0-5 R^e, and $-(CH_2)_n$-heterocyclyl substituted with 0-5 R^e; or R^a and R^a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted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

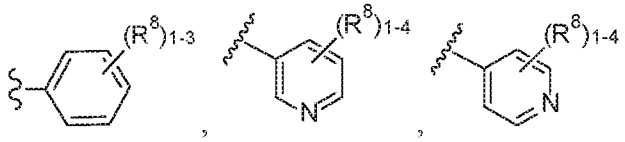
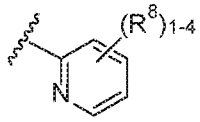
n is independently selected from zero, 1, 2, and 3.

In a ninth aspect, the present invention provides compounds of Formula (VII), or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first, sixth, seventh, and eighth aspects, wherein

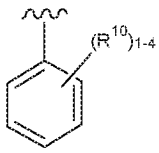
R^2 is independently selected from $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  , $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

R^4 is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH_2(CH_3)_2$;

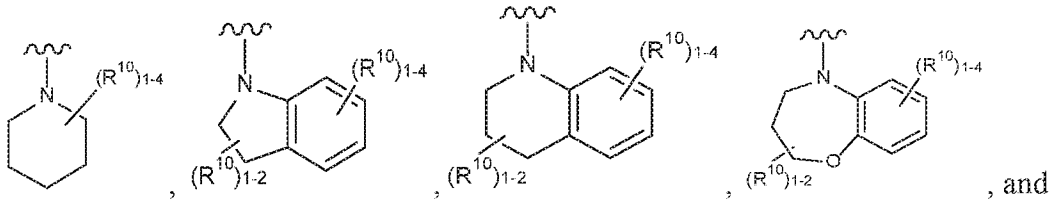
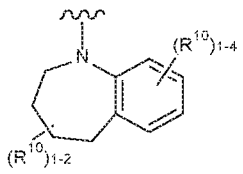
R^5 is R^6;

R^6 is independently selected from  , and  ;

R^8 is independently selected from H, F, Cl, and Br;

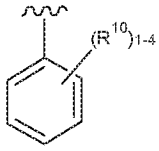
R^9 is  ;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from

 , and  ; and

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

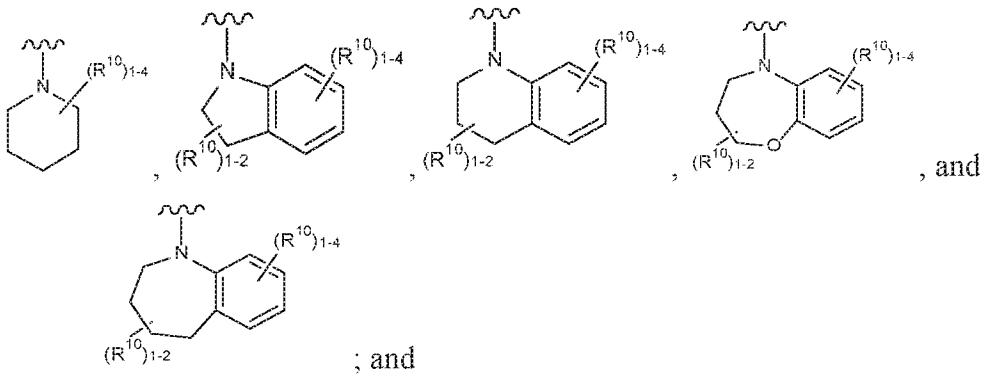
In a tenth aspect, the present invention provides compounds of Formula (VII), or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first, sixth, seventh, eighth, and ninth aspects, wherein

R^9 is  ; and

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

In an eleventh aspect, the present invention provides compounds of Formula (VII), or stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, within the scope of the first, sixth, seventh, eighth, and ninth aspects, wherein

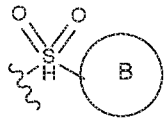
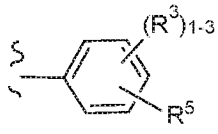
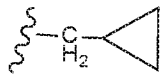
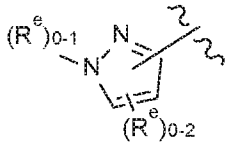
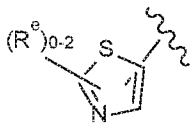
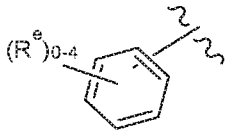
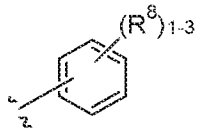
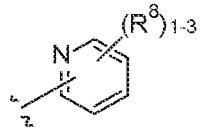
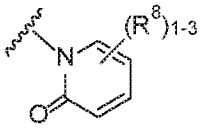
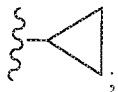
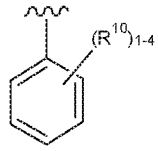
R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from

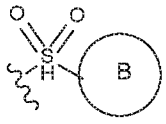
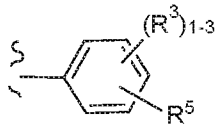
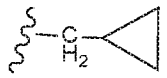
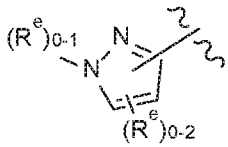
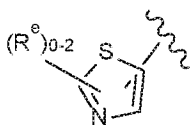
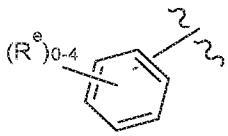
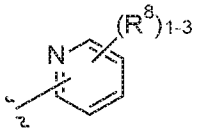
 , and

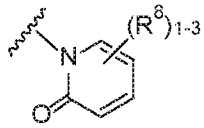
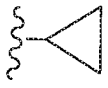
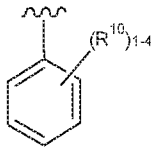
 ; and

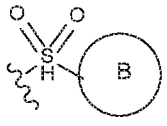
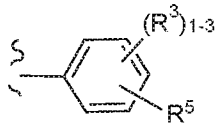
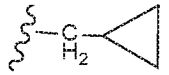
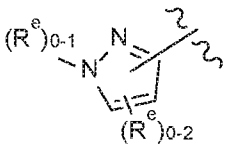
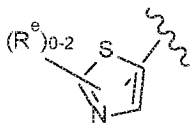
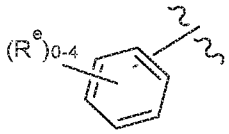
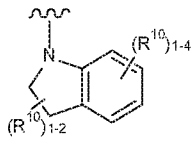
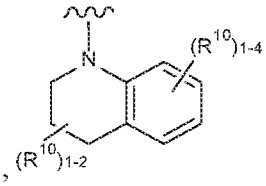
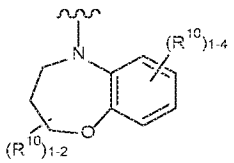
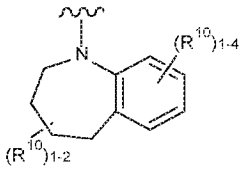
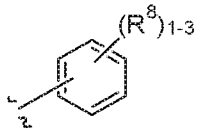
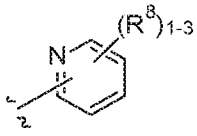
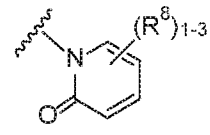
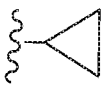
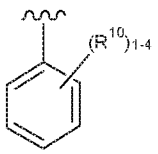
R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

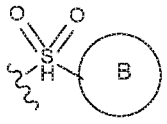
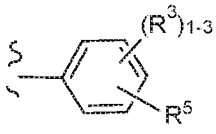
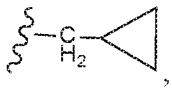
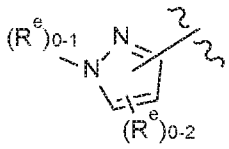
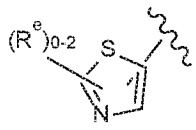
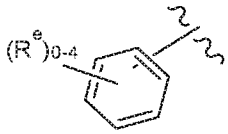
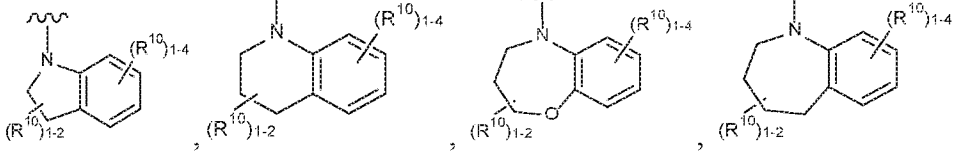
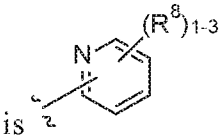
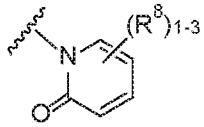
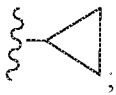
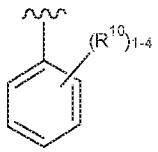
The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be 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.

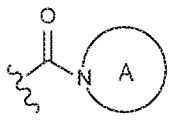
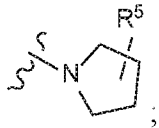
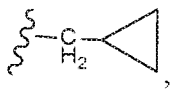
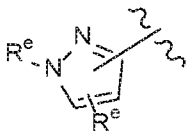
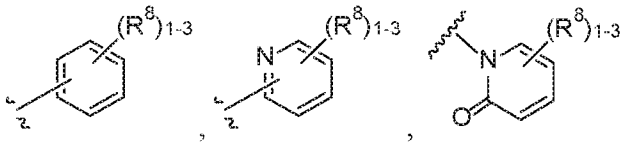
For example, in one non-limiting embodiment, R^1 is  ; ring B is  ; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  ,  ,  or  ; R^3 is H, F, Cl, or Br; R^4 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, or $-CH_2(CH_3)_2$; R^5 is R^6; R^6 is  ,  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  R^{10} is H, F, Cl, CN, or $-CH_3$, or $-OCH_3$; R^e is H or $-CH_3$.

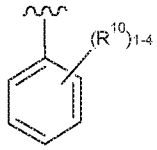
In another non-limiting embodiment, R^1 is  ; ring B is  ; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  ,  ,  or  ; R^3 is H; R^4 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, or $-CH_2(CH_3)_2$; R^5 is R^6; R^6 is  ,

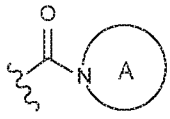
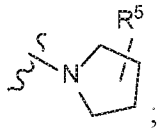
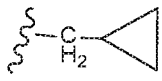
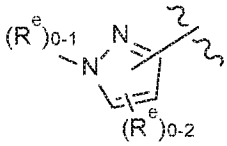
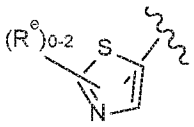
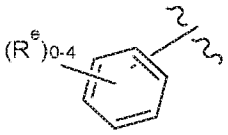
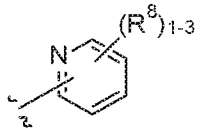
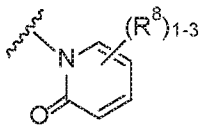
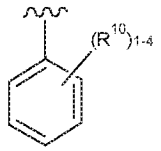

, or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  ; R^{10} is H, F, Cl, CN, or $-CH_3$, or $-OCH_3$; R^e is H or $-CH_3$.

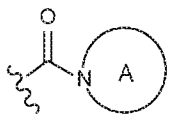
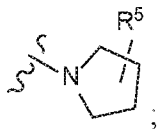
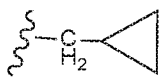
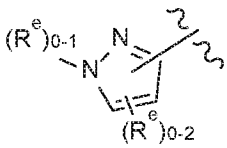
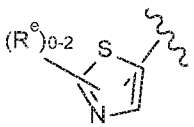
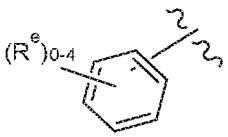
In another non-limiting embodiment, R^1 is  ; ring B is  ; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  ,  ,  , or  ; R^3 is H, F, Cl, or Br; R^4 and R^9 together form a heterocyclic ring selected from  ,  ,  , and  ; R^5 is R^6; R^6 is  ,  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  R^{10} is H, F, Cl, CN, or $-CH_3$, or $-OCH_3$; R^e is H or $-CH_3$.

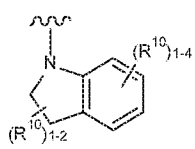
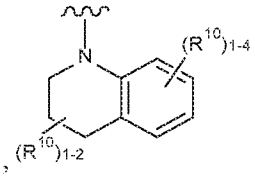
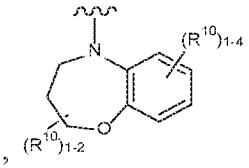
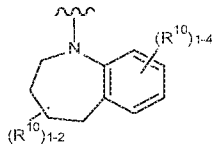
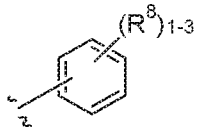
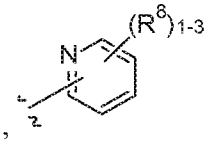
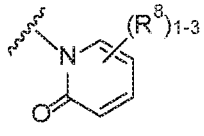
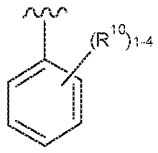
In another non-limiting embodiment, R^1 is  ; ring B is  ; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  ,  ,  , or  ; R^3 is H; R^4 and R^9 together form a heterocyclic ring selected from  ; R^5 is R^6; R^6 is  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  ; R^{10} is H, F, Cl, CN, or $-CH_3$, or $-OCH_3$; R^e is H or $-CH_3$.

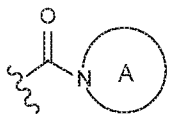
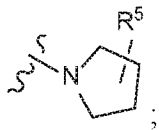
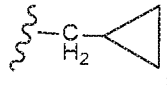
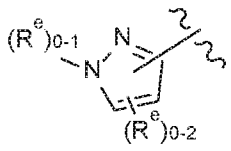
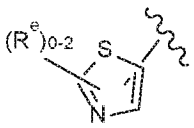
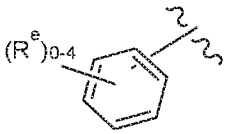
In another non-limiting embodiment, R^1 is  ; ring A is  ; R^2 is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$,  ,  , or  ; R^3 is H, F, Cl, or Br; R^4 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, or $-CH_2(CH_3)_2$; R^5 is R^6; R^6 is  ; R^8 is H, F, Cl, or Br; R^{10} is H, F, Cl, CN, or $-CH_3$, or $-OCH_3$; R^e is H or $-CH_3$.

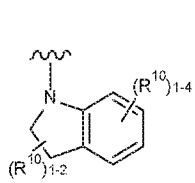
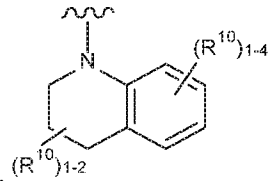
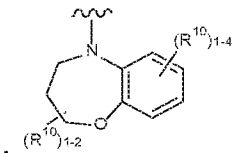
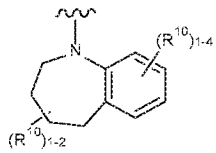
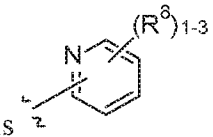
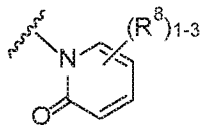
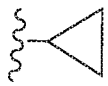
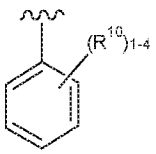
R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  R^{10} is H, F, Cl, CN, or -CH_3, or -OCH_3; R^e is H or –CH_3.

In another non-limiting embodiment, R^1 is  ; ring A is  ; R^2 is -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$,  ,  ,  or  ; R^3 is H; R^4 is -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, or -$CH_2(CH_3)_2$; R^5 is R^6; R^6 is  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  ; R^{10} is H, F, Cl, CN, or -CH_3, or -OCH_3; R^e is H or –CH_3.

In another non-limiting embodiment, R^1 is  ; ring A is  ; R^2 is -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$,  ,  ,  or  ; R^3 is H, F, Cl, or Br; R^4 and R^9 together form a heterocyclic ring selected from

 ,  ,  , and  ; R^5 is R^6; R^6 is  ,  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  R^{10} is H, F, Cl, CN, or -CH_3, or -OCH_3; R^e is H or –CH_3.

In another non-limiting embodiment, R^1 is  ; ring A is  ; R^2 is -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$,  ,  ,  or  ; R^3 is H; R^4 and R^9 together form a heterocyclic ring selected from

 ,  ,  , and  ; R^5 is R^6; R^6 is  ,  , or  ; R^8 is H, F, Cl, Br, C_{1-4} alkyl, or $C(=O)NH_2$; R^9 is  ; R^{10} is H, F, Cl, CN, or -CH_3, or -OCH_3; R^e is H or –CH_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.

In another aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another aspect, the present invention provides a compound selected from

(*S*)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 001

(*S*)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 002

1-(4-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one, 003

6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(ethyl(phenyl)amino)pyridine-2,4-diol, 004

3-((2-butyl-5-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile, 005

(6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 006

(S)-(6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 007

(R)-(6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 008

(R)-(6-butyl-2,4-dihydroxy-5-(indolin-1-yl)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 009

3-((4-bromophenyl)sulfonyl)-6-butyl-5-(methyl(phenyl)amino)pyridine-2,4-diol, 010

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol, 011

6-butyl-3-((4-(6-fluoropyridin-3-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol, 012

6-butyl-5-(indolin-1-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 013

6-butyl-5-(methyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 014

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol, 015

6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol, 016

6-butyl-5-(methyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 017

1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-chloropyridin-2(1H)-one, 018

(S)-(6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 019

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)pyridine-2,4-diol, 020

6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 021

6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, , 022

(R)-(6-butyl-2,4-dihydroxy-5-(isopropyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 023

6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 024

6-butyl-5-(isopropyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 025

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)pyridine-2,4-diol, 026

6-butyl-5-(isopropyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 027

6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 028

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((3-methoxyphenyl)(methyl)amino)pyridine-2,4-diol, 029

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((3-methoxyphenyl)(methyl)amino)pyridine-2,4-diol, 030

6-butyl-5-((3-methoxyphenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 031

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((4-methoxyphenyl)(methyl)amino)pyridine-2,4-diol, 032

6-butyl-5-((4-methoxyphenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 035

(S)-(6-butyl-2,4-dihydroxy-5-((4-methoxyphenyl)(methyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 036

6-butyl-5-((4-methoxyphenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 037

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((4-methoxyphenyl)(methyl)amino)pyridine-2,4-diol, 038

6-butyl-5-((3-methoxyphenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 039

6-butyl-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 040

6-butyl-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 042

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol, 044

(6-butyl-2,4-dihydroxy-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridin-3-yl)((S)-3-phenylpyrrolidin-1-yl)methanone, 045

6-butyl-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 046

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol, 047

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol, 048

6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 049

6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 050

6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 051

6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 052

(6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 053

4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 054

4'-((6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 055

4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 056

4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 057

5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 058

5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol, 059

4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 060

4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 061

4'-((6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 062

5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol, 063

5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 064

4'-((6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 065

(R)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 066

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)methanone, 067

(S)-(6-butyl-2,4-dihydroxy-5-(phenyl(propyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 068

(R)-(6-butyl-2,4-dihydroxy-5-(phenyl(propyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone, 069

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 070

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 071

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 072

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone, 073

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(4-(2,3-dichlorobenzyl)piperazin-1-yl)methanone, 074

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(2-fluorophenyl)pyrrolidin-1-yl)methanone, 075

(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)methanone, 076

3-((4-bromophenyl)sulfonyl)-6-butyl-5-(ethyl(phenyl)amino)pyridine-2,4-diol, 077

6-butyl-5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 078

6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 079

6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 080

6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-methoxypyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 081

1-(4-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)phenyl)-5-chloropyridin-2(1H)-one, 082

4'-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carbonitrile, 083

6-butyl-5-(ethyl(phenyl)amino)-3-(phenylsulfonyl)pyridine-2,4-diol, 084

4'-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 085

6-butyl-5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 086

6-butyl-5-(ethyl(phenyl)amino)-3-((2'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)sulfonyl)pyridine-2,4-diol, 087

3-([1,1'-biphenyl]-4-ylsulfonyl)-6-butyl-5-(ethyl(phenyl)amino)pyridine-2,4-diol, 088

6-butyl-5-(methyl(m-tolyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 090

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(m-tolyl)amino)pyridine-2,4-diol, 091

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(p-tolyl)amino)pyridine-2,4-diol, 092

3-((4-bromophenyl)sulfonyl)-6-butyl-5-(methyl(m-tolyl)amino)pyridine-2,4-diol, 093

6-butyl-5-(methyl(p-tolyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 094

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(methyl(m-tolyl)amino)pyridine-2,4-diol, 095

6-butyl-5-(methyl(m-tolyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 096

6-butyl-5-(methyl(p-tolyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 097

1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(p-tolyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one, 098

1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(m-tolyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one, 099

6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(methyl(p-tolyl)amino)pyridine-2,4-diol, 100

6-butyl-5-((3-fluorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 101

6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 102

6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 103

6-butyl-5-((3-fluorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 104

6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 105

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((3-fluorophenyl)(methyl)amino)pyridine-2,4-diol, 106

6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 107

6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 108

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((3-fluorophenyl)(methyl)amino)pyridine-2,4-diol, 109

6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 110

6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 111

6-butyl-5-((2-fluorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 112

3-((2-butyl-4,6-dihydroxy-5-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridin-3-yl)(methyl)amino)benzonitrile, 113

5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol, 114

6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 115

6-butyl-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol, 116

3-((2-butyl-5-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile, 117

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((2-fluorophenyl)(methyl)amino)pyridine-2,4-diol, 118

3-((2-butyl-4,6-dihydroxy-5-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridin-3-yl)(methyl)amino)benzonitrile, 119

5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol, 120

5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol, 122

6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 123

6-butyl-5-((2-fluorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 124

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((2-fluorophenyl)(methyl)amino)pyridine-2,4-diol, 125

6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol, 126

6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 127

6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol, 128

6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 129

(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)methanone, 130

3-((4-bromophenyl)sulfonyl)-5-(ethyl(phenyl)amino)-6-(m-tolyl)pyridine-2,4-diol, 131

(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)methanone, 132

6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 133

3-((4-bromophenyl)sulfonyl)-6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)pyridine-2,4-diol, 134

6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol, 135

6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol, 136

4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 137

4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 138

4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 139

4'-((6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 140

4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 141

4'-((6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide, 142

4'-((6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 143

4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide, 144

4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 145

4'-((6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide, 146

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
CAN	acetonitrile
Alk	alkyl

BBr_3	boron tribromide
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
t-BuOH	*tert*-butanol
Cbz	carbobenzyloxy
$CDCl_3$	deutero-chloroform
CD_3OD	deutero-methanol
CDI	1,1′-carbonyldiimidazole
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CO_2	carbon dioxide
DCM	dichloromethane
DIEA, DIPEA or Hunig's base	diisopropylethylamine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
Et_3N or TEA	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
K_2CO_3	potassium carbonate
K_2HPO_4	potassium hydrogenphosphate

LCMS	liquid chromatography mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
LG	leaving group
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
MsOH or MSA	methylsulfonic acid
NaCl	sodium chloride
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OAc	ammonium acetate
$Pd(OAc)_2$	palladium(II) acetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PG	protecting group
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
i-PrOH or IPA	isopropanol
Rt	retention time
SiO_2	silica oxide
SFC	supercritical fluid chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
T3P®	1-propanephosphonic acid cyclic anhydride

Synthesis

The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples.

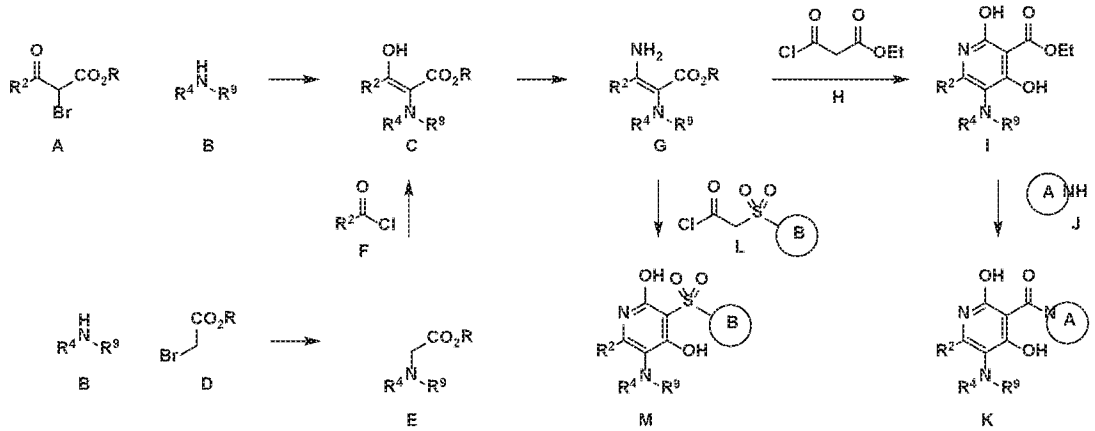
Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); Smith, M.B. et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. 6th Edition, Wiley & Sons, New York, NY (2007); Katritzky, A.R. et al, eds., *Comprehensive Organic Functional Groups Transformations II*, 2nd Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1999), and references therein.

Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Wiley and Sons (1991)).

Scheme 1



Initial condensation of bromoketoester **A** with amine **B** yields intermediate **C**. Alternatively, compound **C** can be prepared by the alkylation of amine **B** with bromoacetate **D** followed by condensation of intermediate **E** with acid chloride **F**. Intermediate **C** can be converted to the amine intermediate **G**. Acylation with acid chloride **L** followed by cyclization yields sulfone compounds of general structure **M**. Alternatively, condensation of **G** with compound **H** yields compound **I** after cyclization. Amide formation with **J** yields compounds of the general structure **K**.

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).

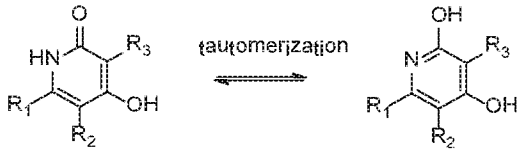
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

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.

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.

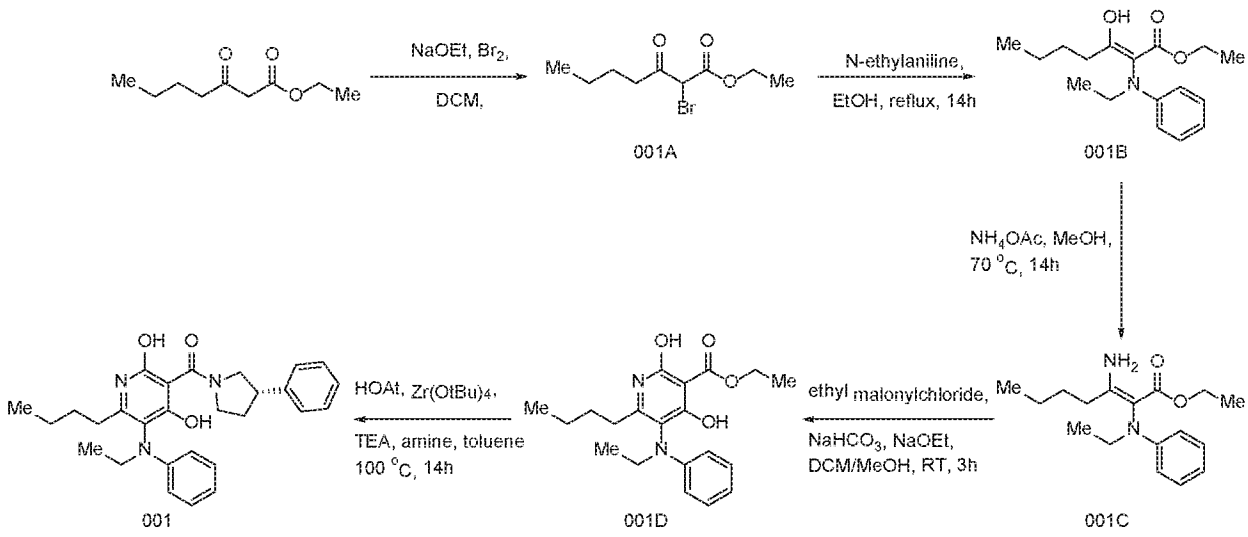


Description of Analytical LCMS methods:

Method A: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm particles; Mobile Phase A: water with 0.05% TFA; Mobile Phase B: ACN with 0.05% 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.

Example 001: (*S*)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone



Example 001A: ethyl 2-bromo-3-oxoheptanoate

Sodium ethoxide (10.8 ml, 29.0 mmol) was dissolved in EtOH (58.1 ml). Ethyl 3-oxoheptanoate (5.15 ml, 29.0 mmol) was added followed by dropwise addition of bromine (1.50 ml, 29.0 mmol). After 1 hour, the reaction was diluted with water and extracted twice with DCM. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient from 0 to 30% EtOAc in hexanes) to yield **Example 001A** (6.56 g, 26.1 mmol, 90%) as a clear oil. LC/MS (Method A) RT = 0.96 min, MS (ESI) *m/z*: 251.0 $(M+H)^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ 4.78 (s, 1H), 4.28 (q, *J*=7.1 Hz, 2H), 2.75 (td, *J*=7.3, 3.4 Hz, 2H), 1.65 - 1.53 (m, 3H), 1.31 (t, *J*=7.0 Hz, 3H), 0.98 - 0.86 (m, 4H).

Example 001B: (*E*)-ethyl 2-(ethyl(phenyl)amino)-3-hydroxyhept-2-enoate

Example 001A (1.35 g, 5.37 mmol) and N-ethylaniline (0.650 g, 5.37 mmol) were dissolved in EtOH (10.73 ml) and heated to reflux for 14h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with water, washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, 80 g silica gel column, 29 minute gradient from 0 to 100% DCM in hexanes) to yield **Example 001B** (0.876 g, 3.01 mmol, 56.0%) LC/MS (Method A) RT = 1.23 min, MS (ESI) *m/z*: 292.3$(M+H)^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ 12.60 (s, 1H), 7.22 - 7.15 (m, 2H), 6.73 - 6.67 (m, 1H), 6.63 (dd, *J*=8.8, 0.9 Hz, 2H), 4.25 - 4.12 (m, 2H), 3.51 - 3.32 (m, 2H), 2.37 - 2.21 (m,

2H), 1.28 - 1.24 (m, 2H), 1.19 (t, *J*=7.2 Hz, 3H), 1.12 (t, *J*=7.2 Hz, 3H), 0.98 - 0.89 (m, 2H), 0.84 (t, *J*=7.3 Hz, 3H)

Example 001C: (*E*)-ethyl 3-amino-2-(ethyl(phenyl)amino)hept-2-enoate

Example 001B (0.943 g, 3.24 mmol) and ammonium acetate (2.50 g, 32.4 mmol) were dissolved in MeOH (16.18 ml). The reaction mixture was allowed to stir at 50 °C for 14h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc and water. The layers were separated and the organic layer was washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ISCO, dry load, 80 g silica gel column, 29 minute gradient from 0 to 100% EtOAc in hexanes) to yield **Example 001C** (0.552 g, 1.90 mmol, 58.7 % yield) as a pale yellow oil. LC/MS (Method A) RT = 1.068 min, MS (ESI) m/z: 291.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.20 - 7.06 (m, 2H), 6.79 - 6.49 (m, 3H), 4.28 - 3.90 (m, 2H), 3.59 - 3.23 (m, 2H), 2.32 - 2.18 (m, 2H), 1.50 - 1.38 (m, 2H), 1.36 - 1.22 (m, 4H), 1.22 - 1.15 (m, 3H), 1.11 - 1.05 (m, 3H), 0.87 - 0.81 (m, 3H).

Example 001D: ethyl 6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxynicotinate

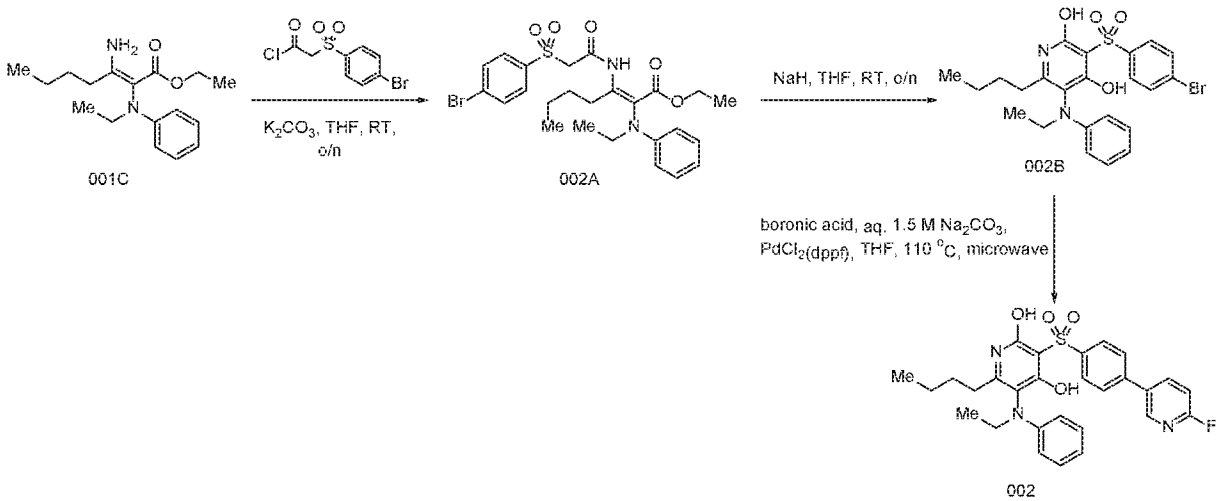
Example 001C (0.348 g, 1.20 mmol) was dissolved in DCM (5.99 ml) and sodium bicarbonate (5.99 ml, 5.99 mmol) added. Ethyl malonylchloride (0.453 ml, 3.60 mmol) was dissolved in 0.5 mL DCM and added dropwise. The reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was diluted with saturated NH_4Cl and washed thrice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added EtOH (5.99 ml) and sodium ethoxide (1.790 ml, 4.79 mmol). The reaction mixture was allowed to stir at ambient temperature overnight and concentrated under reduced pressure. The residue was diluted with 1 N HCl and DCM. The layers were separated and the aqueous layer was back extracted with DCM (x2). The combined organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on ISCO using 80g column eluting with EtOAc in DCM 0-100% to yield **Example 001D** (0.225 g, 0.628 mmol, 52.4 % yield). LC/MS (Method A) RT = 0.968 min, MS (ESI) *m/z*: 359.1 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 13.66 (br. s., 1H), 10.37 (br. s., 1H), 7.24 - 7.13 (m, 2H), 6.75 (t, *J*=7.3 Hz, 1H), 6.64 - 6.56 (m, 2H), 4.43 (q, *J*=7.2 Hz, 2H), 3.57 (dd, *J*=9.9, 7.3 Hz, 2H), 2.66 - 2.47 (m, 2H),

1.65 - 1.57 (m, 2H), 1.41 (t, *J*=7.0 Hz, 3H), 1.39 - 1.30 (m, 2H), 1.23 (t, *J*=7.2 Hz, 3H), 0.86 (t, *J*=7.4 Hz, 3H).

Example 001: (*S*)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone

To a solution of **Example 001D** (0.015 g, 0.042 mmol) and (*S*)-3-phenylpyrrolidine hydrochloride (7.7 mg, 0.042 mmol) in toluene (0.697 ml) was added TEA (0.012 ml, 0.084 mmol). The reaction mixture was stirred for 5 min. To the stirred reaction was added HOAt (3.4 mg, 0.025 mmol) followed zirconium(IV) *tert*-butoxide (9.8 µl, 0.025 mmol). The reaction was stirred at 100 °C for 14h. The reaction mixture was quenched by the addition of 1N HCl (3 mL) at RT. The reaction mixture was extracted with DCM. The combined organic layers were dried and concentrated, the residue was dissolved in DMF and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 001** (0.0084 g, 0.018 mmol, 42.8 % yield): LC/MS (Method A) RT = 0.973 min, MS (ESI) *m/z*: 460.2 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.33 (br. s., 4H), 7.24 (br. s., 1H), 7.14 (br. s., 2H), 6.64 (br. s., 1H), 6.55 (d, *J*=8.0 Hz, 2H), 4.01 - 3.35 (m, 4H), 3.17 (d, *J*=4.8 Hz, 1H), 2.55 (s, 2H), 2.34 - 1.89 (m, 4H), 1.41 (br. s., 2H), 1.20 - 1.06 (m, 5H), 0.71 (br. s., 3H)) (2 exchangeable protons were not observed). Human APJ cAMP Potency range B.

Example 002: (*S*)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone



Example 002A: (*E*)-ethyl 3-(2-((4-bromophenyl)sulfonyl)acetamido)-2-(ethyl(phenyl)amino)hept-2-enoate

Example 001C (532 mg, 1.83 mmol) was dissolved in THF (18.300 ml) and potassium carbonate (1270 mg, 9.16 mmol) was added to the reaction mixture. 2-((4-bromophenyl)sulfonyl)acetyl chloride (1090 mg, 3.66 mmol) was added, and the reaction mixture was allowed to stir for 14h. The reaction mixture was diluted with saturated NH_4Cl and extracted thrice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, 40 g silica gel column, 19 minute gradient from 0 to 50% EtOAc in hexanes) to yield **Example 002A** (0.668 g, 1.21 mmol, 66.1 % yield) as a yellow solid. LC/MS (Method A) RT = 1.10 min, MS (ESI) *m/z*: 551.1 $(M+H)^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ 11.90 (s, 1H), 7.88 - 7.82 (m, 2H), 7.73 (d, *J*=8.8 Hz, 2H), 7.20 (dd, *J*=8.8, 7.5 Hz, 2H), 6.74 (t, *J*=7.3 Hz, 1H), 6.58 (dd, *J*=8.7, 1.0 Hz, 2H), 4.13 (s, 2H), 4.12 - 4.05 (m, 2H), 3.41 (d, *J*=5.9 Hz, 2H), 2.86 - 2.71 (m, 2H), 1.35 - 1.23 (m, 4H), 1.21 (t, *J*=7.2 Hz, 3H), 1.05 (t, *J*=7.0 Hz, 3H), 0.85 - 0.72 (m, 3H).

Example 002B: 3-((4-bromophenyl)sulfonyl)-6-butyl-5-(ethyl(phenyl)amino)pyridine-2,4-diol

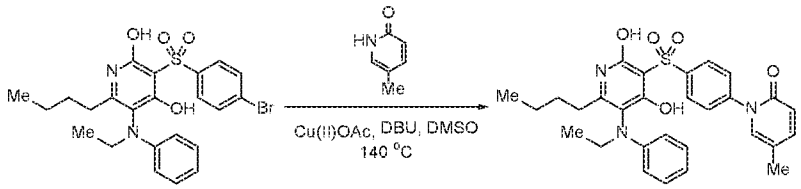
Example 002A (688 mg, 1.25 mmol) was dissolved in THF (25.600 ml). Sodium hydride (100 mg, 2.50 mmol, 60% dispersion in mineral oil) was added, and the reaction mixture was allowed to stir for 14h at ambient temperature. The reaction mixture was diluted with EtOAc and washed with 1 N HCl, water, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, 24 g silica gel column, 19 minute gradient from 0 to 100% EtOAc in hexanes) to yield **Example 002B** (309 mg, 0.611 mmol, 49.0 % yield). LC/MS (Method A) RT = 1.09 min, MS (ESI) *m/z*: 505.0 $(M+H)^+$. ^1H NMR (500MHz, CHLOROFORM-d) δ 11.53 (s, 1H), 10.64 (br. s., 1H), 7.96 (d, *J*=8.5 Hz, 2H), 7.67 (d, *J*=8.5 Hz, 2H), 7.28 - 7.25 (m, 2H), 6.85 (t, *J*=7.3 Hz, 1H), 6.62 (d, *J*=7.7 Hz, 2H), 2.72 - 2.41 (m, 2H), 1.63 - 1.59 (m, 2H), 1.43 - 1.24 (m, 5H), 0.96 - 0.79 (m, 5H).

Example 002: 6-butyl-5-(ethyl(phenyl)amino)-3-((4-(6-fluoropyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol

Example 002B (15 mg, 0.030 mmol), (6-fluoropyridin-3-yl)boronic acid (13 mg, 0.089 mmol), and $PdCl_2$(dppf)-CH_2Cl_2Adduct (2.42 mg, 2.97 μmol) were dissolved in THF

(848 µl) and 1.5 M aq. sodium carbonate (59 µl, 0.089 mmol) was added. The reaction mixture was degassed with nitrogen for 10 minutes. The reaction mixture was then sealed and heated under microwave irradiation for 30 minutes at 110 °C. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min to yield **Example 002** (9.8 mg, 0.018 mmol, 62 % yield): LC/MS (Method A) RT = 1.07 min, MS (ESI) *m/z*: 522.2 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.60 (br. s., 1H), 8.34 (br. s., 1H), 8.00 (d, *J*=8.0 Hz, 2H), 7.84 (d, *J*=7.8 Hz, 2H), 7.32 (d, *J*=6.3 Hz, 1H), 7.06 (t, *J*=7.6 Hz, 2H), 6.55 (t, *J*=6.9 Hz, 1H), 6.48 (d, *J*=8.0 Hz, 2H), 2.33 - 2.11 (m, 2H), 1.40 (br. s., 2H), 1.23 (s, 2H), 1.16 (d, *J*=7.2 Hz, 2H), 1.08 (t, *J*=7.0 Hz, 3H), 0.72 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed). Human APJ cAMP Potency range A.

Example 003: 1-(4-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one

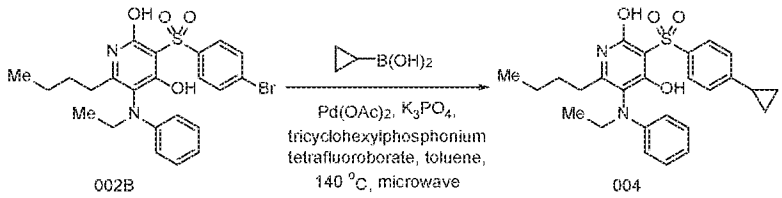


002B 003

Example 002B (18 mg, 0.035 mmol), 5-methylpyridin-2(1H)-one (7.6 mg, 0.069 mmol), and copper (II) acetate (6.3 mg, 0.035 mmol) were dissolved in DMSO (989 µL) and DBU (10 µL, 0.069 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. The reaction mixture was sealed and heated to 140 °C and allowed to stir for 14h. The residue was diluted in DMSO, filtered, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-55% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 003** (10.1 mg, 0.0190 mmol, 54.1 % yield): LC/MS (Method A) RT = 1.01 min, MS (ESI) *m/z*: 534.2 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.28 - 7.80 (m, 2H), 7.56 - 7.28 (m,

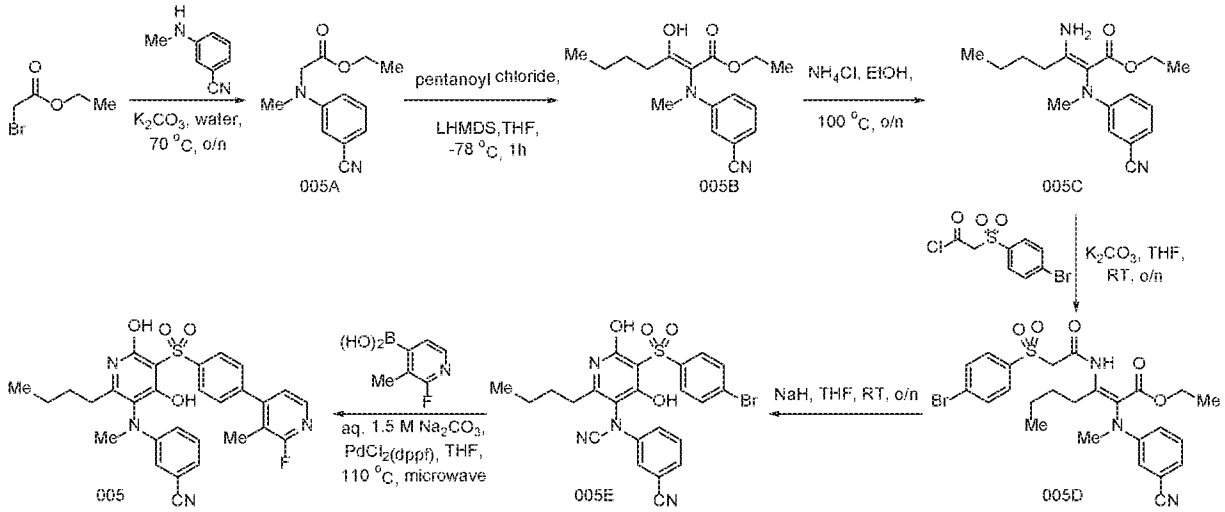
5H), 7.03 (br. s., 2H), 6.44 (d, *J*=8.8 Hz, 3H), 3.94 - 3.06 (m, 2H), 2.30 - 2.10 (m, 2H), 2.05 (s, 3H), 1.39 (br. s., 2H), 1.21 - 0.99 (m, 5H), 0.73 (br. s., 3H) (2 exchangeable protons were not observed). Human APJ cAMP Potency range A.

Example 004: 6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(ethyl(phenyl)amino)pyridine-2,4-diol



Example 002B (17.5 mg, 0.0350 mmol), cyclopropylboronic acid (17.8 mg, 0.208 mmol), $PdOAc_2$ (3.11 mg, 0.0140 mmol), tricyclohexylphosponium tetrafluoroborate (10.20 mg, 0.0280 mmol), and tripotassium phosphate (29.4 mg, 0.138 mmol) were dissolved in toluene (989 µl) and degassed with nitrogen for 10 minutes. The reaction mixture vessel was sealed and heated for 60 minutes under microwave irradiation at 140 °C. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 004** (5.4 mg, 0.011 mmol, 33 % yield): LC/MS (Method A) RT = 1.11 min, MS (ESI) *m/z*: 467.2 $(M+H)^+$. ^1H NMR (600MHz, DMSO-d_6) δ 7.84 (d, *J*=7.1 Hz, 2H), 7.36 - 7.24 (m, 2H), 7.14 (br. s., 2H), 6.66 (br. s., 1H), 6.60 - 6.51 (m, 2H), 2.44 - 2.20 (m, 2H), 2.07 (s, 1H), 1.51 (br. s., 1H), 1.44 - 1.35 (m, 3H), 1.19 - 1.11 (m, 4H), 1.06 (d, *J*=6.9 Hz, 2H), 0.86 (s, 1H), 0.80 (br. s., 2H), 0.72 (t, *J*=7.4 Hz, 3H) (2 exchangeable protons were not observed). Human APJ cAMP Potency range A.

Example 005: 3-((2-butyl-5-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile



Example 005A: ethyl 2-((3-cyanophenyl)(methyl)amino)acetate

Ethyl 2-bromoacetate (0.50 mL, 4.5 mmol), 3-(methylamino)benzonitrile (0.596 g, 4.51 mmol), and potassium carbonate (3.12 g, 22.5 mmol) were dissolved in Water (12.88 mL) and heated to 70 °C for 14h. Reaction was diluted with water and EtOAc. The layers were separated and the organic layer was washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The residue was purified on ISCO using a 40 g column eluting with 0-100% EtOAc in hexanes to yield ethyl **Example 005A** (0.600 g, 2.75 mmol, 61.0 % yield) as a pale yellow oil. LC/MS (Method A) RT = 1.01 min, MS (ESI) *m/z*: 219.1 $(M+H)^+$. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.33 - 7.29 (m, 1H), 7.03 (d, *J*=7.4 Hz, 1H), 6.91 - 6.89 (m, 1H), 6.80 - 6.79 (m, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 4.09 (s, 2H), 3.11 (s, 3H), 1.29 (t, *J*=7.0 Hz, 3H).

Example 005B: ethyl 2-((3-cyanophenyl)(methyl)amino)-3-oxoheptanoate

Example 005A (0.245 g, 1.12 mmol) was dissolved in THF (11.23 ml) and cooled to -78 °C. To the cooled solution was added LHMDS (0.133 mL, 1.12 mmol) and the reaction mixture was allowed to stir for 25 min. Pentanoyl chloride (0.133 ml, 1.12 mmol) was added, and the reaction mixture was allowed to slowly warm to ambient temperature over 1 hour. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic layer was washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified on ISCO using 0-100% EtOAc in hexanes on a 40 g column to yield **Example 005B** (0.150 g, 0.496 mmol, 44.2 % yield) as a colorless oil. LC/MS (Method A) RT = 1.30 min, MS (ESI) *m/z*: 303.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 12.34 (s, 1H), 7.17 (d, *J*=7.9 Hz,

1H), 6.93 (dt, *J*=7.6, 1.0 Hz, 1H), 6.80 - 6.76 (m, 1H), 6.76 - 6.72 (m, 1H), 4.17 - 3.97 (m, 2H), 2.98 (s, 3H), 2.27 - 2.12 (m, 2H), 1.54 - 1.47 (m, 2H), 1.23 (dt, *J*=15.0, 7.5 Hz, 2H), 1.05 (t, *J*=7.0 Hz, 3H), 0.79 (t, *J*=7.4 Hz, 3H).

Example 005C: (*E*)-ethyl 3-amino-2-((3-cyanophenyl)(methyl)amino)hept-2-enoate

Example 005B (0.150 g, 0.496 mmol) and ammonium acetate (0.765 g, 9.92 mmol) were dissolved in EtOH (4.96 ml) and heated to 100 °C. The reaction mixture was stirred overnight. The reaction mixture was concentrated and dissolved in EtOAc and water. The layers were separated and the organic layer was washed with water, washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified on ISCO using 40 g column eluting with 0-100% EtOAc in hexanes to yield **Example 005C** (0.137 g, 0.455 mmol, 92 % yield). LC/MS (Method A) RT = 1.27 min, MS (ESI) *m/z*: 302.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.27 - 7.20 (m, 1H), 6.96 (dt, *J*=7.5, 1.1 Hz, 1H), 6.88 - 6.86 (m, 1H), 6.85 - 6.81 (m, 1H), 4.21 - 3.97 (m, 2H), 3.06 (s, 3H), 2.34 - 2.11 (m, 2H), 1.52 - 1.42 (m, 2H), 1.38 - 1.24 (m, 2H), 1.08 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed).

Example 005D: (*E*)-ethyl 3-(2-((4-bromophenyl)sulfonyl)acetamido)-2-((3-cyanophenyl)(methyl)amino)hept-2-enoate

Example 005C (0.137 g, 0.455 mmol) was dissolved in THF (4.55 ml) and potassium carbonate (0.314 g, 2.27 mmol) was added. 2-((4-bromophenyl)sulfonyl)acetyl chloride (0.271 g, 0.909 mmol) was added and the reaction mixture allowed to stir for 14h. The reaction mixture was diluted with saturated NH_4Cl and extracted thrice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, 40 g silica gel column, 19 minute gradient from 0 to 50% EtOAc in hexanes) to yield **Example 005D** (0.205 g, 0.364 mmol, 80 % yield). LC/MS (Method A) RT = 1.24 min, MS (ESI) *m/z*: 562.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.88 - 7.85 (m, 2H), 7.79 - 7.75 (m, 2H), 7.32 - 7.29 (m, 1H), 7.09 - 7.05 (m, 1H), 6.85 - 6.83 (m, 1H), 6.79 (dd, *J*=8.0, 2.3 Hz, 1H), 4.18 - 4.15 (m, 2H), 4.14 (d, *J*=2.4 Hz, 1H), 3.07 (s, 3H), 2.89 - 2.65 (m, 2H), 1.43 - 1.24 (m, 6H), 1.08 (t, *J*=7.0 Hz, 3H), 0.84 (t, *J*=7.3 Hz, 3H).

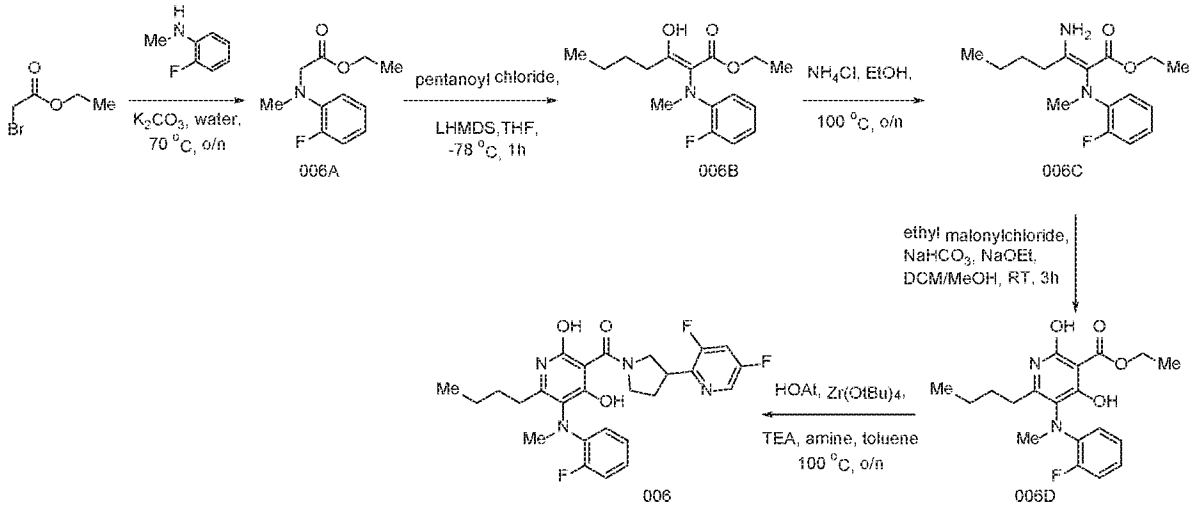
Example 005E: 3-((5-((4-bromophenyl)sulfonyl)-2-butyl-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile

Example 005D (205 mg, 0.364 mmol) was dissolved in THF (6.00 ml). Sodium hydride (29.2 mg, 0.729 mmol, 60% dispersion in mineral oil) was added and the reaction was allowed to stir overnight. The reaction was diluted with EtOAc and washed with 1 N HCl, water, then brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (ISCO, 24 g silica gel column, 19 minute gradient from 0 to 100% EtOAc in hexanes) to yield **Example 005E** (0.122 g, 0.236 mmol, 64.8 % yield). LC/MS (Method A) RT = 1.15 min, MS (ESI) *m/z*: 516.1 $(M+H)^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ 11.60 (s, 1H), 10.92 - 10.74 (m, 1H), 7.95 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.39 - 7.30 (m, 1H), 7.12 (d, *J*=7.9 Hz, 1H), 6.89 - 6.84 (m, 1H), 6.80 (dd, *J*=8.0, 2.3 Hz, 1H), 3.22 (s, 3H), 2.59 - 2.40 (m, 2H), 1.66 - 1.58 (m, 2H), 1.43 - 1.32 (m, 2H), 0.92 (t, *J*=7.3 Hz, 3H).

Example 005: 3-((2-butyl-5-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile

Example 005E (15 mg, 0.029 mmol), (2-fluoro-3-methylpyridin-4-yl)boronic acid (13.50 mg, 0.08700 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (2.37 mg, 2.90 µmol) were dissolved in THF (830 µL) and 1.5 M aqueous sodium carbonate (58.1 µL, 0.0870 mmol) was added. The reaction mixture was degassed with nitrogen for 10 minutes. The reaction mixture vessel was then sealed and heated under microwave irradiation for 30 minutes at 110 °C. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-55% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield AB-005 (11 mg, 0.020 mmol, 69 % yield): LC/MS (Method A) RT = 1.03 min, MS (ESI) *m/z*: 547.0 $(M+H)^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.17 - 8.09 (m, 1H), 8.01 (d, *J*=7.6 Hz, 2H), 7.54 (d, *J*=7.6 Hz, 2H), 7.26 (br. s., 2H), 6.97 (d, *J*=7.3 Hz, 1H), 6.83 - 6.73 (m, 2H), 3.02 (s, 3H), 2.15 (s, 5H), 1.40 (br. s., 2H), 1.24 - 1.13 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed). Human APJ cAMP Potency range A.

Example 006: (6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone



Example 006A: benzyl 2-((2-fluorophenyl)(methyl)amino)acetate

Benzyl 2-bromoacetate (0.50 mL, 3.2 mmol), 2-fluoro-N-methylaniline (0.399 g, 3.19 mmol), and potassium carbonate (2.202 g, 15.93 mmol) were dissolved in water (9.11 mL) and heated to 70 °C for 14h. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic layer was washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The residue was purified on ISCO 0-100% EtOAc in hexanes on a 40 g column to yield **Example 006A** (0.750 g, 2.33 mmol, 73.2 % yield). Compound 006A was used without further purification. LC/MS (Method A) RT = 1.14 min, MS (ESI) *m/z*: 274.1 $(M+H)^+$.

Example 006B: benzyl 2-((2-fluorophenyl)(methyl)amino)-3-oxoheptanoate

Example 006A (0.750 g, 2.74 mmol) was dissolved in THF (27.4 ml) and cooled to -78 °C. To the cooled solution was added LHMDS (5.49 ml, 5.49 mmol). The reaction mixture was allowed to stir for 25 min and pentanoyl chloride (0.326 ml, 2.74 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to ambient temperature over 1 hour. The reaction mixture was diluted with water and EtOAc. The layers were separated and the organic layer was washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified on ISCO using 80g column eluting with 0-100% EtOAc in hexanes to yield **Example 006B** (0.202 g, 0.565 mmol, 21%). LC/MS (Method A) RT = 1.34 min, MS (ESI) *m/z*: 358.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 12.04 (s, 1H), 7.10 - 7.07 (m, 2H), 6.93 (ddd, *J*=4.3, 3.2, 2.2 Hz, 2H), 6.78 (d, *J*=8.1 Hz, 3H), 6.63 - 6.53 (m, 2H), 5.01 (d,

J=5.1 Hz, 2H), 2.92 (d, *J*=2.2 Hz, 3H), 2.37 - 2.17 (m, 2H), 1.49 - 1.32 (m, 2H), 1.22 - 1.07 (m, 2H), 0.71 (t, *J*=7.3 Hz, 3H).

Example 006C. (*E*)-benzyl 3-amino-2-((2-fluorophenyl)(methyl)amino)hept-2-enoate

Example 006B (0.561 g, 1.57 mmol) and ammonium acetate (2.42 g, 31.4 mmol) were dissolved in EtOH (15.70 ml) and heated to 100 °C. The reaction mixture was allowed to stir for 14h. The reaction mixture was concentrated and dissolved in EtOAc and water. The layers were separated and the organic layer was washed with water, washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified on ISCO using 40 g column eluting with 0-100% EtOAc in hexanes to yield **Example 006C** (0.332 g, 0.931 mmol, 59.3 % yield). LC/MS (Method A) RT = 1.29 min, MS (ESI) *m/z*: 357.2 $(M+H)^+$. ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.28 - 7.21 (m, 4H), 7.11 (dd, *J*=7.3, 2.3 Hz, 2H), 6.97 - 6.90 (m, 2H), 6.76 - 6.71 (m, 1H), 6.71 - 6.66 (m, 2H), 5.12 (d, *J*=9.6 Hz, 2H), 3.13 (d, *J*=3.0 Hz, 3H), 2.51 - 2.31 (m, 2H), 1.54 - 1.46 (m, 2H), 1.39 - 1.32 (m, 2H), 0.89 (t, *J*=7.3 Hz, 3H).

Example 006D: ethyl 6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxynicotinate

Example 006C (0.100 g, 0.281 mmol) was dissolved in DCM (1.403 ml) and sodium bicarbonate (1.403 ml, 1.403 mmol) was added. Ethyl malonyl chloride (0.106 ml, 0.842 mmol) was dissolved in 0.5 mL DCM and added dropwise. The reaction mixture was stirred at ambient temperature for 14h. The reaction mixture was diluted with saturated NH_4Cl and washed thrice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added EtOH (1.403 ml) and sodium ethoxide (0.419 ml, 1.12 mmol). The reaction mixture was allowed to stir at ambient temperature over 14h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with 1 N HCl and DCM. The layers were separated and the aqueous layer was back extracted with DCM x2. The combined organic layer was washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified on ISCO using 80g column eluting with EtOAc in DCM 0-100% to yield **Example 006D** (0.041 g, 0.113 mmol, 40.3 % yield). LC/MS (Method A) RT = 1.13 min, MS (ESI) *m/z*: 363.2 $(M+H)^+$. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 13.76 (s, 1H), 10.15 - 9.68 (m, 1H), 7.07 - 7.01 (m, 1H), 6.96

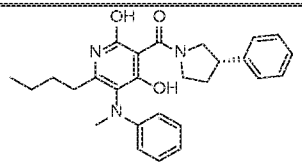
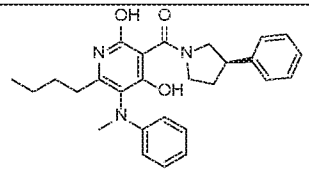
(ddd, *J*=13.8, 8.0, 1.3 Hz, 1H), 6.89 - 6.76 (m, 2H), 4.53 - 4.39 (m, 2H), 3.23 (d, *J*=1.8 Hz, 3H), 2.77 - 2.51 (m, 2H), 1.67 - 1.59 (m, 2H), 1.44 (t, *J*=7.0 Hz, 3H), 1.39 - 1.30 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H).

Example 006: (6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone

To a solution of **Example 006D** (0.025 g, 0.069 mmol) and 3,5-difluoro-2-(pyrrolidin-3-yl)pyridine (0.013 g, 0.069 mmol) in toluene (1.150 ml) was added TEA (0.019 ml, 0.14 mmol). The reaction mixture was stirred for 5 min. To the stirred reaction mixture was added HOAt (5.63 mg, 0.0410 mmol) followed zirconium(IV) *t*-butoxide (0.016 ml, 0.041 mmol). The reaction mixture was stirred at 100 °C for 14 h. The mixture was quenched by the addition of 1N HCl (3 mL) at ambient temperature. The reaction mixture was extracted with DCM. The combined organic layers were dried and concentrated under reduced vacuum. The residue was dissolved in DMF, filtered, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-70% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to yield **Example 006** (4.1 mg, 8.2 μmol, 12 % yield). LC/MS (Method A) RT = 0.95 min, MS (ESI) *m/z*: 501.3 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (br. s., 1H), 7.92 (br. s., 1H), 7.05 (br. s., 4H), 3.91 (s, 1H), 3.85 - 3.49 (m, 4H), 3.07 (s, 3H), 2.26 (d, *J*=7.3 Hz, 4H), 1.46 - 1.06 (m, 4H), 0.71 (t, *J*=6.9 Hz, 3H) (2 exchangeable protons were not observed). Human APJ cAMP Potency range A.

The compounds listed in the table below were synthesized using the above described methods.

Table 1

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
007		(S)-(6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) ™ 7.31 (m, 4H), 7.23 (d, *J*=7.9 Hz, 1H), 7.16 - 7.06 (m, 2H), 6.62 (t, *J*=6.4 Hz, 1H), 6.51 (m, 2H), 3.64 (m, 2H), 3.54 - 3.29 (m, 2H), 3.04 (m, 3H), 2.22 (m, 3H), 2.00 - 1.84 (m, 2H), 1.40 (m, 2H), 1.15 (m, 2H), 0.72 (m, 3H) (2 exchangeable protons not observed)	0.99 A 446.4	B
008		(R)-(6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.31 (m, 4H), 7.23 (m, 1H), 7.10 (m, 2H), 6.60 (m, 1H), 6.51 (m, 2H), 3.92 - 3.67 (m, 1H), 3.64 - 3.29 (m, 1H), 3.04 (m, 3H), 2.55 (s, 3H), 2.22 (m, 3H), 1.94 (m, 1H), 1.41 (m, 2H), 1.17 (m, 2H), 0.74 (m, 3H) (2 exchangeable protons not observed)	0.99 A 446.4	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
009		(R)-(6-butyl-2,4-dihydroxy-5-(indolin-1-yl)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.39 - 7.20 (m, 5H), 7.10 - 7.03 (m, 1H), 6.89 (m, 1H), 6.56 (t, *J*=7.1 Hz, 1H), 6.03 (d, *J*=8.0 Hz, 1H), 3.67 (m, 2H), 3.57 - 3.32 (m, 2H), 3.08 (m, 2H), 2.49 - 2.42 (m, 2H), 2.40 - 2.19 (m, 3H), 2.07 - 1.88 (m, 2H), 1.47 (m, 2H), 1.25 - 1.14 (m, 2H), 0.76 (m, 3H) (2 exchangeable protons not observed)	0.98 A 458.2	B
010		3-((4-bromophenyl)sulfonyl)-6-butyl-5-(methyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.85 (d, *J*=8.3 Hz, 2H), 7.17 (t, *J*=7.7 Hz, 2H), 6.69 (t, *J*=7.2 Hz, 1H), 6.57 (d, *J*=8.0 Hz, 2H), 3.09 (s, 3H), 2.37 - 2.26 (m, 2H), 1.41 (dt, *J*=15.1, 7.5 Hz, 2H), 1.22 - 1.14 (m, 2H), 0.73 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.02 A 491/493	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
011		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.13 (d, *J*=4.6 Hz, 1H), 8.07 (d, *J*=7.8 Hz, 2H), 7.61 (d, *J*=7.8 Hz, 2H), 7.27 (d, *J*=4.6 Hz, 1H), 7.11 (t, *J*=7.4 Hz, 2H), 6.62 (t, *J*=6.9 Hz, 1H), 6.52 (d, *J*=7.7 Hz, 2H), 3.04 (s, 3H), 2.23 (br. s., 2H), 2.15 (s, 3H), 1.41 (dd, *J*=15.0, 7.3 Hz, 2H), 1.23 - 1.11 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.00 A 522.2	A
012		6-butyl-3-((4-(6-fluoropyridin-3-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.62 (br. s., 1H), 8.40 - 8.33 (m, 1H), 8.07 (d, *J*=8.2 Hz, 2H), 7.91 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=6.5 Hz, 1H), 7.13 (t, *J*=7.7 Hz, 2H), 6.64 (t, *J*=7.1 Hz, 1H), 6.53 (d, *J*=8.0 Hz, 2H), 3.06 (s, 3H), 2.25 (d, *J*=6.9 Hz, 2H), 1.41 (dd, *J*=15.4, 7.9 Hz, 2H), 1.22 - 1.10 (m, 2H), 0.74 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.00 A 508.1	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
013		6-butyl-5-(indolin-1-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.40 (d, *J*=4.3 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=8.1 Hz, 2H), 7.25 (d, *J*=4.8 Hz, 1H), 6.96 (d, *J*=6.9 Hz, 1H), 6.83 - 6.77 (m, 1H), 6.49 - 6.43 (m, 1H), 5.86 (d, *J*=7.8 Hz, 1H), 3.82 - 3.74 (m, 2H), 2.35 (d, *J*=13.1 Hz, 2H), 2.29 - 2.23 (m, 2H), 2.20 (br. s., 3H), 1.45 - 1.36 (m, 2H), 1.19 (dt, *J*=14.7, 7.4 Hz, 2H), 0.78 - 0.70 (m, 3H) (2 exchangeable protons not observed)	0.87 A 516.3	A
014		6-butyl-5-(methyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (br. s., 2H), 7.97 (d, *J*=7.9 Hz, 2H), 7.48 (d, *J*=7.8 Hz, 2H), 7.26 (br. s., 1H), 7.04 (t, *J*=7.6 Hz, 2H), 6.52 (t, *J*=7.0 Hz, 1H), 6.44 (d, *J*=7.9 Hz, 2H), 2.96 (s, 3H), 2.24 (s, 3H), 2.12 (t, *J*=7.4 Hz, 2H), 1.38 (d, *J*=5.4 Hz, 2H), 1.22 - 1.12 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.97 A 504.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
015		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.08 (d, *J*=8.2 Hz, 2H), 7.87 (t, *J*=8.1 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 2H), 7.16 (t, *J*=7.8 Hz, 2H), 7.11 (dd, *J*=8.2, 2.7 Hz, 1H), 6.67 (t, *J*=7.3 Hz, 1H), 6.56 (d, *J*=8.2 Hz, 2H), 3.09 (s, 3H), 2.38 (s, 3H), 2.34 - 2.24 (m, 2H), 1.49 - 1.32 (m, 2H), 1.25 - 1.12 (m, 2H), 0.74 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.01 A 522.1	A
016		6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(methyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.75 (d, *J*=8.2 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 7.05 (t, *J*=7.6 Hz, 2H), 6.54 (t, *J*=7.1 Hz, 1H), 6.44 (d, *J*=7.9 Hz, 2H), 2.96 (s, 3H), 2.13 (t, *J*=7.4 Hz, 2H), 1.95 (m, 1H), 1.37 (d, *J*=5.0 Hz, 2H), 1.19 - 1.13 (m, 2H), 0.99 (d, *J*=6.6 Hz, 2H), 0.77 - 0.68 (m, 5H) (2 exchangeable protons not observed)	1.62 B 453.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
017		6-butyl-5-(methyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (d, *J*=3.9 Hz, 1H), 8.10 (d, *J*=8.1 Hz, 2H), 7.71 - 7.63 (m, 3H), 7.35 (dd, *J*=7.3, 5.0 Hz, 1H), 7.17 (t, *J*=7.7 Hz, 2H), 6.69 (t, *J*=7.1 Hz, 1H), 6.58 (d, *J*=8.1 Hz, 2H), 3.10 (s, 3H), 2.44 (s, 3H), 2.37 - 2.23 (m, 2H), 1.51 - 1.36 (m, 2H), 1.25 - 1.13 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.82 A 504.2	A
018		1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-chloropyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 8.01 (d, *J*=8.2 Hz, 2H), 7.96 (d, *J*=2.6 Hz, 1H), 7.59 (dd, *J*=9.9, 2.8 Hz, 1H), 7.52 (d, *J*=8.2 Hz, 2H), 7.06 (t, *J*=7.7 Hz, 2H), 6.58 - 6.50 (m, 2H), 6.46 (d, *J*=8.1 Hz, 2H), 2.97 (s, 3H), 2.13 (t, *J*=7.7 Hz, 2H), 1.39 (br. s., 2H), 1.21 - 1.10 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.40 B 540.1	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
019		(S)-(6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.33 (d, *J*=5.0 Hz, 4H), 7.27 - 7.22 (m, 1H), 6.93 (d, *J*=7.3 Hz, 1H), 6.85 (t, *J*=7.3 Hz, 1H), 6.52 (t, *J*=7.2 Hz, 1H), 6.14 - 6.05 (m, 1H), 3.79 - 3.48 (m, 6H), 3.22 (d, *J*=5.2 Hz, 1H), 2.88 - 2.69 (m, 2H), 2.39 - 2.31 (m, 2H), 2.26 (m, 1H), 2.08 - 1.88 (m, 3H), 1.46 (m, 2H), 1.28 - 1.16 (m, 2H), 0.77 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.07 A 472.3	B
020		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.14 (d, *J*=4.8 Hz, 1H), 8.09 (br. s., 2H), 7.67 (br. s., 2H), 7.29 (d, *J*=4.6 Hz, 1H), 7.13 (br. s., 2H), 6.64 (br. s., 1H), 6.56 (br. s., 2H), 4.12 (br. s., 1H), 4.05 - 3.87 (m, 2H), 2.43 - 2.20 (m, 2H), 2.16 (s, 3H), 1.46 - 1.31 (m, 2H), 1.23 (s, 3H), 1.14 (br. s., 6H) (2 exchangeable protons not observed)	1.12 A 550.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
021		6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.07 (d, *J*=7.7 Hz, 2H), 7.87 (t, *J*=8.2 Hz, 1H), 7.64 (br. s., 2H), 7.11 (d, *J*=8.3 Hz, 1H), 6.93 (d, *J*=6.7 Hz, 1H), 6.86 (br. s., 1H), 6.52 (br. s., 1H), 6.12 (d, *J*=7.9 Hz, 1H), 2.83 - 2.70 (m, 2H), 2.38 (s, 3H), 2.36 - 2.24 (m, 2H), 2.03 - 1.88 (m, 2H), 1.53 - 1.40 (m, 2H), 1.28 - 1.17 (m, 4H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.10 A 548.2	A
022		6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.46 (d, *J*=5.0 Hz, 1H), 7.99 - 7.93 (m, 2H), 7.46 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=5.0 Hz, 1H), 6.81 (d, *J*=7.2 Hz, 1H), 6.75 - 6.68 (m, 1H), 6.36 (td, *J*=7.2, 0.8 Hz, 1H), 6.08 - 6.01 (m, 1H), 3.58 - 3.50 (m, 1H), 3.06 - 2.99 (m, 1H), 2.81 - 2.61 (m, 2H), 2.24 (s, 3H), 2.20 - 2.09 (m, 2H), 1.97 - 1.82 (m, 2H), 1.42 ((dtt, *J*=11.3, 7.5, 3.6 Hz, 2H), 1.21 (sxt, *J*=7.4 Hz, 2H), 0.78 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.90 A 530.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
023		(R)-(6-butyl-2,4-dihydroxy-5-(isopropyl(phenyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.39 - 7.18 (m, 5H), 7.07 (br. s., 2H), 6.61 - 6.45 (m, 3H), 4.18 - 3.23 (m, 3H), 2.35 - 2.13 (m, 3H), 1.98 - 1.82 (m, 4H), 1.42 (br. s., 2H), 1.19 - 1.03 (m, 8H), 0.71 (d, *J*=6.3 Hz, 3H) (2 exchangeable protons not observed)	1.98 B 474.2	B
024		6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, *J*=4.1 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 2H), 7.72 - 7.62 (m, 3H), 7.36 (dd, *J*=7.4, 5.0 Hz, 1H), 6.94 (d, *J*=7.3 Hz, 1H), 6.88 (t, *J*=7.7 Hz, 1H), 6.55 (t, *J*=7.3 Hz, 1H), 6.14 (d, *J*=8.1 Hz, 1H), 3.50 (br. s., 1H), 3.29 - 3.17 (m, 1H), 2.88 - 2.66 (m, 2H), 2.44 (s, 3H), 2.41 - 2.30 (m, 2H), 2.04 - 1.88 (m, 2H), 1.50 - 1.37 (m, 2H), 1.21 (dq, *J*=14.6, 7.2 Hz, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.89 A 530.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
025		6-butyl-5-(isopropyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, *J*=3.8 Hz, 1H), 8.05 (d, *J*=8.0 Hz, 2H), 7.66 (dd, *J*=17.3, 7.8 Hz, 3H), 7.35 (dd, *J*=7.4, 4.8 Hz, 1H), 7.13 (t, *J*=7.6 Hz, 2H), 6.64 (t, *J*=6.9 Hz, 1H), 6.57 (d, *J*=8.2 Hz, 2H), 4.12 (br. s., 1H), 2.43 (s, 3H), 2.39 (d, *J*=18.1 Hz, 1H), 2.25 (br. s., 1H), 1.48 - 1.30 (m, 2H), 1.13 (dd, *J*=14.0, 6.3 Hz, 8H), 0.69 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.90 A 532.2	A
026		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 11.82 (s, 1H), 11.32 (br. s., 1H), 8.12 - 8.06 (m, 2H), 7.91 (t, *J*=8.2 Hz, 1H), 7.72 - 7.66 (m, 2H), 7.19 - 7.12 (m, 3H), 6.68 (t, *J*=7.2 Hz, 1H), 6.61 (d, *J*=8.1 Hz, 2H), 4.17 (dt, *J*=12.8, 6.4 Hz, 1H), 2.46 - 2.38 (m, 4H), 2.34 - 2.25 (m, 1H), 1.50 - 1.32 (m, 2H), 1.21 - 1.09 (m, 8H), 0.70 (t, *J*=7.3 Hz, 3H)	1.11 A 550.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
027		6-butyl-5-(isopropyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (br. s., 1H), 8.45 (d, *J*=4.5 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=7.9 Hz, 2H), 7.24 (d, *J*=4.8 Hz, 1H), 7.03 (t, *J*=7.7 Hz, 2H), 6.51 (t, *J*=7.0 Hz, 1H), 6.46 (d, *J*=8.2 Hz, 2H), 3.95 (br. s., 1H), 2.26 - 2.03 (m, 5H), 1.46 - 1.33 (m, 2H), 1.20 - 1.11 (m, 2H), 1.09 (d, *J*=6.1 Hz, 3H), 0.99 (d, *J*=6.2 Hz, 3H), 0.71 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.91 A 532.2	A
028		6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.11 (d, *J*=4.8 Hz, 1H), 8.01 (d, *J*=8.1 Hz, 2H), 7.52 (d, *J*=8.1 Hz, 2H), 7.25 (d, *J*=4.8 Hz, 1H), 6.84 (d, *J*=7.3 Hz, 1H), 6.76 (t, *J*=7.6 Hz, 1H), 6.41 (t, *J*=7.2 Hz, 1H), 6.06 (d, *J*=8.3 Hz, 1H), 3.57 - 3.45 (m, 1H), 3.10 - 3.03 (m, 1H), 2.81 - 2.63 (m, 2H), 2.20 (t, *J*=7.6 Hz, 2H), 2.14 (s, 3H), 1.98 - 1.84 (m, 2H), 1.46 - 1.38 (m, 2H), 1.20 (sxt, *J*=7.3 Hz, 2H), 0.77 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.10 A 548.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
029		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((3-methoxyphenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.13 (d, *J*=4.8 Hz, 1H), 8.02 (d, *J*=7.7 Hz, 2H), 7.55 (d, *J*=7.2 Hz, 2H), 7.27 (d, *J*=4.8 Hz, 1H), 6.97 (t, *J*=8.1 Hz, 1H), 6.18 (d, *J*=7.0 Hz, 1H), 6.09 (d, *J*=7.6 Hz, 1H), 5.99 (br. s., 1H), 3.17 (br. s., 3H), 2.99 (br. s., 3H), 2.16 (s, 5H), 1.40 (d, *J*=6.2 Hz, 2H), 1.22 - 1.16 (m, 2H), 0.77 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.10 A 552.2	A
030		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((3-methoxyphenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.09 (d, *J*=8.0 Hz, 2H), 7.88 (t, *J*=8.1 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 2H), 7.12 (d, *J*=6.1 Hz, 1H), 7.06 (t, *J*=8.1 Hz, 1H), 6.30 (d, *J*=7.6 Hz, 1H), 6.15 (d, *J*=7.8 Hz, 1H), 6.07 (br. s., 1H), 3.51 (br. s., 3H), 3.08 (s, 2H), 2.42 - 2.23 (m, 5H), 1.43 (d, *J*=7.7 Hz, 2H), 1.23 - 1.14 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.10 A 552.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
031		6-butyl-5-((3-methoxyphenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (br. s., 1H), 8.46 (br. s., 1H), 7.97 (d, *J*=7.7 Hz, 2H), 7.50 (d, *J*=7.6 Hz, 2H), 7.25 (d, *J*=4.5 Hz, 1H), 6.95 (t, *J*=8.0 Hz, 1H), 6.15 (d, *J*=7.1 Hz, 1H), 6.07 (d, *J*=8.0 Hz, 1H), 5.97 (br. s., 1H), 3.17 (br. s., 3H), 2.96 (s, 3H), 2.25 (s, 3H), 2.14 (br. s., 2H), 1.47 - 1.36 (m, 2H), 1.23 - 1.14 (m, 2H), 0.77 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	0.91 A 534.2	B
032		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((4-methoxyphenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.08 (d, *J*=8.0 Hz, 2H), 7.88 (t, *J*=8.1 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 2H), 7.12 (d, *J*=6.4 Hz, 1H), 6.78 (d, *J*=8.7 Hz, 2H), 6.51 (d, *J*=8.7 Hz, 2H), 3.47 (br. s., 3H), 3.05 (s, 3H), 2.38 (s, 3H), 2.31 (d, *J*=8.0 Hz, 2H), 1.42 (br. s., 2H), 1.26 - 1.16 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.10 A 552.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
035		6-butyl-5-((4-methoxyphenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, *J*=4.0 Hz, 1H), 8.04 (d, *J*=8.2 Hz, 2H), 7.66 (d, *J*=7.3 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 2H), 7.36 - 7.30 (m, 1H), 6.75 (d, *J*=8.9 Hz, 2H), 6.47 (d, *J*=8.5 Hz, 2H), 3.17 (s, 3H), 3.03 (s, 3H), 2.43 (s, 3H), 2.26 (d, *J*=7.9 Hz, 2H), 1.42 (dd, *J*=15.6, 7.6 Hz, 2H), 1.25 - 1.14 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.90 A 534.2	B
036		(S)-(6-butyl-2,4-dihydroxy-5-((4-methoxyphenyl)(methyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.32 (m, 4H), 7.24 (m, 1H), 6.76 (m, 2H), 6.48 (m, 2H), 3.89 (br. s., 1H), 3.75 - 3.60 (m, 6H), 3.53 (m, 1H), 3.03 (br. s., 3H), 2.25 (m, 3H), 1.96 (m, 1H), 1.41 (m, 2H), 1.18 (m, 2H), 0.75 (m, 3H) (2 exchangeable protons not observed)	1.05 A 476.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
037		6-butyl-5-((4-methoxyphenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.49 (d, *J*=4.4 Hz, 1H), 8.08 (d, *J*=7.9 Hz, 2H), 7.64 (d, *J*=7.7 Hz, 2H), 7.29 (d, *J*=4.6 Hz, 1H), 6.77 (d, *J*=8.7 Hz, 2H), 6.50 (d, *J*=8.6 Hz, 2H), 3.65 (s, 3H), 3.04 (s, 3H), 2.29 (m, 2H), 2.26 (s, 3H), 1.42 (m, 2H), 1.25 - 1.15 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	0.91 A 534.2	A
038		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((4-methoxyphenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.14 (d, *J*=4.9 Hz, 1H), 8.11 (d, *J*=8.2 Hz, 2H), 7.67 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=4.9 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 2H), 6.51 (d, *J*=8.8 Hz, 2H), 3.17 (s, 3H), 3.05 (s, 3H), 2.30 (br. s., 2H), 2.16 (s, 3H), 1.42 (dd, *J*=13.5, 6.6 Hz, 2H), 1.25 - 1.15 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.09 A 552.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
039		6-butyl-5-((3-methoxyphenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, *J*=4.4 Hz, 1H), 8.08 (d, *J*=8.1 Hz, 2H), 7.71 - 7.61 (m, 3H), 7.35 (dd, *J*=7.4, 4.9 Hz, 1H), 7.05 (t, *J*=8.1 Hz, 1H), 6.28 (d, *J*=7.7 Hz, 1H), 6.15 (d, *J*=8.2 Hz, 1H), 6.08 (br. s., 1H), 3.68 (s, 3H), 3.08 (s, 3H), 2.44 (s, 3H), 2.34 - 2.24 (m, 2H), 1.50 - 1.37 (m, 2H), 1.27 - 1.15 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.91 A 534.2	A
040		6-butyl-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.61 - 8.38 (m, 3H), 7.99 (d, *J*=7.9 Hz, 2H), 7.51 (d, *J*=7.3 Hz, 2H), 7.25 (d, *J*=4.6 Hz, 1H), 6.66 (br. s., 1H), 6.56 (d, *J*=7.9 Hz, 1H), 5.97 (d, *J*=7.9 Hz, 1H), 3.52 (br. s., 1H), 2.76 - 2.60 (m, 2H), 2.29 - 2.15 (m, 5H), 2.09 (s, 3H), 1.98 - 1.81 (m, 2H), 1.43 (br. s., 2H), 1.28 - 1.18 (m, 2H), 0.78 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.06 A 544.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
042		6-butyl-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (dd, *J*=16.7, 4.1 Hz, 1H), 8.09 (d, *J*=8.1 Hz, 1H), 7.96 (d, *J*=7.9 Hz, 1H), 7.67 (d, *J*=7.6 Hz, 2H), 7.48 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=5.7 Hz, 2H), 6.76 (br. s., 1H), 6.69 (d, *J*=7.8 Hz, 1H), 6.05 (d, *J*=8.2 Hz, 1H), 2.83 - 2.61 (m, 2H), 2.46 - 2.40 (m, 3H), 2.38 - 2.29 (m, 2H), 2.12 (s, 3H), 2.04 - 1.91 (m, 2H), 1.52 - 1.39 (m, 2H), 1.28 - 1.18 (m, 3H), 0.77 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.05 A 544.3	B
044		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 (d, *J*=5.0 Hz, 1H), 8.12 (d, *J*=7.7 Hz, 2H), 7.68 (d, *J*=7.2 Hz, 2H), 7.31 (d, *J*=5.0 Hz, 1H), 6.76 (s, 1H), 6.68 (d, *J*=8.0 Hz, 1H), 6.05 (d, *J*=8.0 Hz, 1H), 5.76 (s, 1H), 3.51 (t, *J*=8.9 Hz, 1H), 2.82 - 2.70 (m, 2H), 2.39 - 2.31 (m, 2H), 2.17 (s, 3H), 2.13 (s, 3H), 2.04 - 1.87 (m, 2H), 1.49 - 1.41 (m, 2H), 1.30 - 1.20 (m, 2H), 0.78 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.26 A 562.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
045		(6-butyl-2,4-dihydroxy-5-(4-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridin-3-yl)((S)-3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.40 - 7.18 (m, 6H), 6.71 (m, 2H), 6.06 - 5.91 (m, 1H), 3.59 - 3.47 (m, 1H), 3.35 - 3.06 (m, 2H), 2.82 - 2.61 (m, 2H), 2.27 (m, 3H), 2.10 (br. s., 3H), 2.03 - 1.94 (m, 2H), 1.90 (m, 3H), 1.44 (m, 2H), 1.23 (m, 3H), 0.78 (m, 3H) (2 exchangeable protons not observed)	1.24 A 486.4	A
046		6-butyl-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.68 (br. s., 1H), 8.14 (d, *J*=8.2 Hz, 2H), 7.95 (d, *J*=7.2 Hz, 1H), 7.73 (d, *J*=8.1 Hz, 2H), 7.57 (br. s., 1H), 6.99 (d, *J*=7.0 Hz, 1H), 6.90 (t, *J*=7.5 Hz, 1H), 6.59 (t, *J*=7.2 Hz, 1H), 6.16 (d, *J*=8.1 Hz, 1H), 2.94 - 2.70 (m, 3H), 2.48 - 2.45 (s, 3H), 2.39 - 2.26 (m, 2H), 2.02 (br. s., 1H), 1.76 (br. s., 1H), 1.47 (d, *J*=7.6 Hz, 2H), 1.20 (dt, *J*=15.0, 7.6 Hz, 2H), 1.05 (d, *J*=6.4 Hz, 3H), 0.74 (t, *J*=7.4 Hz, 3H) (2 exchangeable protons were not observed)	1.04 A 544.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
047		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.10 (d, *J*=4.7 Hz, 1H), 7.99 - 7.92 (m, 2H), 7.48 (d, *J*=8.1 Hz, 2H), 7.27 - 7.19 (m, 1H), 6.86 - 6.80 (m, 1H), 6.77 - 6.68 (m, 1H), 6.39 (t, *J*=7.1 Hz, 1H), 6.06 (d, *J*=8.1 Hz, 1H), 3.51 (m, 3H), 2.82 - 2.62 (m, 2H), 2.21 (m, 1H), 2.14 (s, 3H), 1.63 (m, 1H), 1.52 - 1.34 (m, 2H), 1.23 - 1.13 (m, 2H), 0.96 - 0.90 (m, 3H), 0.78 - 0.69 (m, 3H) (2 exchangeable protons were not observed)	1.25 A 562.3	A
048		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 - 8.06 (m, 2H), 7.90 (t, *J*=8.0 Hz, 1H), 7.69 (d, *J*=7.7 Hz, 2H), 7.13 (d, *J*=6.9 Hz, 1H), 6.98 (d, *J*=6.7 Hz, 1H), 6.89 (br. s., 1H), 6.62 - 6.51 (m, 1H), 6.19 - 6.07 (m, 1H), 3.67 (d, *J*=10.8 Hz, 1H), 2.81 (d, *J*=19.2 Hz, 2H), 2.39 (s, 3H), 2.35 - 2.26 (m, 1H), 2.02 (m, 1H), 1.76 (m, 1H), 1.47 (m, 2H), 1.27 - 1.14 (m, 3H), 1.04 (d, *J*=6.1 Hz, 3H), 0.78 - 0.68 (m, 3H) (2 exchangeable protons were not observed)	1.25 A 562.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
049		6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.02 - 7.91 (m, 3H), 7.50 (br. s., 2H), 7.15 (d, *J*=4.4 Hz, 1H), 6.98 (br. s., 2H), 6.49 (br. s., 1H), 6.41 (d, *J*=7.3 Hz, 2H), 3.03 (br. s., 3H), 2.15 - 1.98 (m, 4H), 1.02 - 0.93 (m, 3H), 0.74 (br. s., 1H), 0.21 (br. s., 1H), 0.14 (br. s., 1H), 0.00 (br. s., 1H), -0.16 (br. s., 1H) (2 exchangeable protons were not observed)	1.13 A 534.3	A
050		6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.35 (d, *J*=4.1 Hz, 1H), 7.88 (d, *J*=7.7 Hz, 2H), 7.52 (d, *J*=7.3 Hz, 1H), 7.41 (d, *J*=7.3 Hz, 2H), 7.25 - 7.18 (m, 1H), 6.95 (t, *J*=7.4 Hz, 2H), 6.48 - 6.41 (m, 1H), 6.38 (d, *J*=7.9 Hz, 2H), 3.05 (s, 2H), 2.30 (s, 3H), 2.12 - 1.95 (m, 2H), 0.94 (t, *J*=6.9 Hz, 3H), 0.74 (br. s., 1H), 0.21 (br. s., 1H), 0.16 (br. s., 1H), 0.00 (br. s., 1H), -0.14 (d, *J*=4.7 Hz, 1H) (2 exchangeable protons were not observed)	0.91 A 516.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
051		6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.90 (d, *J*=7.3 Hz, 2H), 7.73 (t, *J*=7.9 Hz, 1H), 7.46 (br. s., 2H), 6.97 (d, *J*=6.9 Hz, 3H), 6.46 (d, *J*=12.5 Hz, 1H), 6.40 (d, *J*=7.2 Hz, 2H), 3.03 (d, *J*=3.4 Hz, 2H), 2.24 (s, 3H), 2.13 - 1.98 (m, 2H), 0.96 (br. s., 3H), 0.78 - 0.70 (m, 1H), 0.20 (br. s., 1H), 0.14 (br. s., 1H), 0.00 (br. s., 1H), -0.15 (br. s., 1H) (2 exchangeable protons were not observed)	1.16 A 534.3	A
052		6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.34 (d, *J*=4.0 Hz, 1H), 7.89 (d, *J*=7.3 Hz, 2H), 7.42 (d, *J*=6.8 Hz, 2H), 7.14 (d, *J*=4.4 Hz, 1H), 6.94 (t, *J*=7.1 Hz, 2H), 6.44 (d, *J*=7.4 Hz, 1H), 6.38 (d, *J*=7.6 Hz, 2H), 3.04 (d, *J*=2.9 Hz, 2H), 2.12 (s, 3H), 2.10 - 1.94 (m, 2H), 0.94 (t, *J*=6.8 Hz, 3H), 0.75 (br. s., 1H), 0.20 (br. s., 1H), 0.15 (br. s., 1H), 0.00 (br. s., 1H), -0.14 (d, *J*=4.1 Hz, 1H) (2 exchangeable protons were not observed)	0.92 A 516.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
053		(6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.36 - 8.21 (m, 1H), 7.69 (t, *J*=8.5 Hz, 1H), 6.92 (m, 2H), 6.37 (m, 3H), 3.83 - 3.69 (m, 3H), 3.61 - 3.37 (m, 2H), 3.29 (m, 2H), 3.20 - 3.02 (m, 1H), 2.04 (m, 3H), 1.07 - 0.87 (m, 3H), 0.74 (m, 1H), 0.29 - 0.11 (m, 2H), 0.00 (m, 1H), -0.13 (m, 1H) (2 exchangeable protons were not observed)	1.09 A 495.3	B
054		4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.04 (d, *J*=8.0 Hz, 2H), 7.61 - 7.48 (m, 5H), 7.39 (d, *J*=7.2 Hz, 1H), 6.94 (d, *J*=7.1 Hz, 1H), 6.87 (t, *J*=7.6 Hz, 1H), 6.54 (t, *J*=7.1 Hz, 1H), 6.14 (d, *J*=8.2 Hz, 1H), 3.35 (m, 2H), 2.80 - 2.70 (m, 2H), 2.55 (s, 6H), 2.35 (m, 2H), 1.95 (m, 2H), 1.48 - 1.40 (m, 2H), 1.23 - 1.17 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.18 A 586.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
055		4'-((6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.03 (d, *J*=4.5 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.44 - 7.39 (m, 1H), 7.36 - 7.27 (m, 5H), 6.93 (t, *J*=7.6 Hz, 2H), 6.42 (t, *J*=6.9 Hz, 1H), 6.36 (d, *J*=8.0 Hz, 2H), 3.33 - 3.16 (m, 2H), 2.47 (d, *J*=4.5 Hz, 3H), 2.06 - 1.92 (m, 2H), 0.93 (t, *J*=7.0 Hz, 3H), 0.74 (m, 1H), 0.27 - 0.16 (m, 2H), 0.00 (m, 1H), -0.11 (m, 1H) (2 exchangeable protons were not observed)	1.15 A 558.3	A
056		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.21 (br. s., 1H), 8.01 (d, *J*=7.5 Hz, 2H), 7.72 (br. s., 1H), 7.55 (d, *J*=7.3 Hz, 3H), 7.50 - 7.39 (m, 3H), 7.13 (d, *J*=7.0 Hz, 2H), 6.68 - 6.59 (m, 3H), 6.29 (br. s., 1H), 3.88 (s, 3H), 3.44 - 3.31 (m, 2H), 2.60 (d, *J*=4.4 Hz, 3H), 1.01 (t, *J*=7.1 Hz, 3H) (2 exchangeable protons were not observed)	1.07 A 584	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
057		4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.92 (d, J=7.7 Hz, 2H), 7.78 (br. s., 1H), 7.53 - 7.42 (m, 5H), 7.38 (d, J=7.5 Hz, 1H), 7.33 (br. s., 1H), 6.85 (d, J=7.2 Hz, 1H), 6.77 (t, J=7.5 Hz, 1H), 6.41 (t, J=7.1 Hz, 1H), 6.06 (d, J=8.1 Hz, 1H), 3.51 (t, J=9.4 Hz, 1H), 3.06 (br. s., 1H), 2.80 - 2.62 (m, 2H), 2.19 (br. s., 2H), 1.94 - 1.82 (m, 2H), 1.40 (d, J=6.8 Hz, 2H), 1.21 - 1.15 (m, 2H), 0.76 (t, J=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.17 A 558.3	A
058		5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.46 (d, J=3.6 Hz, 1H), 7.94 (d, J=8.1 Hz, 2H), 7.65 - 7.58 (m, 2H), 7.44 (d, J=8.1 Hz, 2H), 7.37 - 7.29 (m, 1H), 7.02 (t, J=7.7 Hz, 2H), 6.58 - 6.44 (m, 3H), 6.21 (d, J=1.8 Hz, 1H), 3.89 (s, 3H), 3.37 (q, J=7.0 Hz, 2H), 2.40 (s, 3H), 0.91 (t, J=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.90 A 542.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
059		5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.94 (d, *J*=7.8 Hz, 2H), 7.80 (t, *J*=8.2 Hz, 1H), 7.60 (s, 1H), 7.44 (d, *J*=7.9 Hz, 2H), 7.10 - 6.98 (m, 3H), 6.56 - 6.45 (m, 3H), 6.20 (s, 1H), 3.82 (s, 3H), 3.36 (q, *J*=7.2 Hz, 2H), 2.34 (s, 3H), 0.90 (t, *J*=7.1 Hz, 3H) (2 exchangeable protons were not observed)	1.21 A 560.2	A
060		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.88 (d, *J*=8.0 Hz, 2H), 7.61 (s, 1H), 7.51 (d, *J*=7.7 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=7.2 Hz, 1H), 7.02 (t, *J*=7.6 Hz, 2H), 6.56 - 6.46 (m, 3H), 6.20 (s, 1H), 3.84 (s, 3H), 3.36 (d, *J*=5.4 Hz, 2H), 2.72 (s, 3H), 2.40 (br. s., 3H), 0.91 (t, *J*=7.1 Hz, 3H) (2 exchangeable protons were not observed)	1.14 A 598.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
061		4'-((6-butyl-5-(3,4-dihydroquinolin-1(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.14 (d, *J*=4.5 Hz, 1H), 7.96 - 7.86 (m, 3H), 7.54 - 7.48 (m, 1H), 7.46 - 7.36 (m, 4H), 6.83 (d, *J*=7.1 Hz, 1H), 6.75 (t, *J*=7.4 Hz, 1H), 6.39 (t, *J*=6.9 Hz, 1H), 6.04 (d, *J*=8.1 Hz, 1H), 3.50 (m, 2H), 2.78 - 2.62 (m, 2H), 2.57 (d, *J*=4.5 Hz, 3H), 2.17 (m, 2H), 1.86 (m, 2H), 1.39 (m, 2H), 1.20 - 1.13 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.17 A 572.3	A
062		4'-((6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.79 (d, *J*=7.9 Hz, 2H), 7.44 - 7.39 (m, 1H), 7.38 - 7.33 (m, 2H), 7.30 (d, *J*=7.9 Hz, 2H), 7.23 (d, *J*=7.0 Hz, 1H), 6.92 (t, *J*=7.6 Hz, 2H), 6.40 (t, *J*=7.0 Hz, 1H), 6.35 (d, *J*=7.9 Hz, 2H), 3.31 - 3.15 (m, 2H), 2.44 (s, 6H), 2.05 - 1.92 (m, 2H), 0.93 (t, *J*=7.0 Hz, 3H), 0.74 (m, 1H), 0.26 - 0.13 (m, 2H), 0.01 (m, 1H), -0.11 (m, 1H) (2 exchangeable protons were not observed)	1.20 A 572.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
063		5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.10 (d, *J*=4.9 Hz, 1H), 7.97 (d, *J*=8.2 Hz, 2H), 7.62 (s, 1H), 7.48 (d, *J*=7.9 Hz, 2H), 7.23 (d, *J*=4.9 Hz, 1H), 7.03 (t, *J*=7.5 Hz, 2H), 6.56 - 6.46 (m, 3H), 6.22 (s, 1H), 3.85 (s, 3H), 3.37 (d, *J*=5.8 Hz, 2H), 2.14 (s, 3H), 0.92 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	1.17 A 560.3	A
064		5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (br. s., 1H), 8.45 (br. s., 1H), 7.96 (d, *J*=8.2 Hz, 2H), 7.63 (s, 1H), 7.47 (d, *J*=7.9 Hz, 2H), 7.24 (d, *J*=4.9 Hz, 1H), 7.08 - 6.98 (m, 2H), 6.57 - 6.47 (m, 3H), 6.22 (s, 1H), 3.90 (s, 3H), 3.38 (d, *J*=6.7 Hz, 2H), 2.24 (s, 3H), 0.93 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.92 A 542.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
065		4'-((6-butyl-2,4-dihydroxy-5-(methyl(phenyl)amino)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.98 - 7.88 (m, 2H), 7.74 (br. s., 1H), 7.55 - 7.41 (m, 5H), 7.39 (d, *J*=7.3 Hz, 1H), 7.31 (br. s., 1H), 7.11 - 7.02 (m, 2H), 6.55 (t, *J*=6.9 Hz, 1H), 6.47 (d, *J*=7.9 Hz, 2H), 2.98 (s, 3H), 2.14 (d, *J*=7.3 Hz, 2H), 1.40 (br. s., 2H), 1.21 - 1.14 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.16 A 532.3	A
066		(R)-(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.32 (br. s., 4H), 7.24 (d, *J*=4.6 Hz, 1H), 7.13 (br. s., 2H), 6.64 (br. s., 1H), 6.55 (d, *J*=8.2 Hz, 2H), 4.04 - 3.15 (m, 6H), 2.26 (br. s., 4H), 1.98 (br. s., 1H), 1.41 (br. s., 2H), 1.20 - 1.07 (m, 5H), 0.72 (br. s., 3H) (2 exchangeable protons were not observed)	0.975 A 460.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
067		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (br. s., 1H), 7.88 (d, *J*=6.3 Hz, 1H), 7.44 (br. s., 1H), 7.11 (br. s., 2H), 6.72 - 6.48 (m, 3H), 3.96 - 3.14 (m, 4H), 2.40 - 2.00 (m, 6H), 1.40 (br. s., 3H), 1.19 - 1.06 (m, 5H), 0.71 (t, *J*=6.8 Hz, 3H) (2 exchangeable protons were not observed)	0.925 A 495.2	A
068		(S)-(6-butyl-2,4-dihydroxy-5-(phenyl(propyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.33 (br. s., 4H), 7.16 - 7.05 (m, 3H), 6.71 - 6.61 (m, 1H), 6.54 (d, *J*=8.2 Hz, 2H), 3.94 - 3.62 (m, 2H), 3.60 - 3.29 (m, 1H), 2.50 - 2.38 (m, 2H), 2.35 - 2.19 (m, 4H), 2.17 - 1.90 (m, 2H), 1.61 - 1.50 (m, 2H), 1.41 (br. s., 2H), 1.15 (br. s., 2H), 0.89 (d, *J*=6.7 Hz, 3H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	1.03 A 474.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
069		(R)-(6-butyl-2,4-dihydroxy-5-(phenyl(propyl)amino)pyridin-3-yl)(3-phenylpyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.39 - 7.21 (m, 5H), 7.13 (br. s., 2H), 6.71 - 6.61 (m, 1H), 6.54 (d, *J*=8.0 Hz, 2H), 3.96 - 3.26 (m, 4H), 2.26 (br. s., 5H), 1.62 - 1.50 (m, 2H), 1.41 (br. s., 2H), 1.26 - 1.09 (m, 4H), 0.89 (d, *J*=6.7 Hz, 3H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	1.03 A 474.2	B
070		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.49 (br. s., 1H), 8.07 (br. s., 1H), 7.13 (br. s., 2H), 6.65 (br. s., 1H), 6.54 (br. s., 2H), 3.91 - 3.28 (m, 4H), 2.50 - 2.46 (m, 2H), 2.26 (d, *J*=7.2 Hz, 4H), 2.12 (br. s., 1H), 1.40 (br. s., 2H), 1.23 - 1.04 (m, 5H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	0.979 A 513.1	A
071		((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (br. s., 1H), 7.92 (br. s., 1H), 7.33 - 7.00 (m, 2H), 6.74 - 6.46 (m, 3H), 4.04 - 3.28 (m, 5H), 2.40 - 2.02 (m, 5H), 1.40 (br. s., 3H), 1.19 - 1.06 (m, 5H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	0.955 A 497.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
072		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.49 (br. s., 1H), 8.06 (br. s., 1H), 7.13 (br. s., 2H), 6.65 (br. s., 1H), 6.55 (br. s., 2H), 3.91 - 3.28 (m, 4H), 2.50 - 2.44 (m, 2H), 2.26 (d, *J*=7.2 Hz, 4H), 2.12 (br. s., 1H), 1.40 (br. s., 2H), 1.21 - 1.04 (m, 5H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	1.00 A 513.2	A
073		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (br. s., 1H), 7.92 (br. s., 1H), 7.26 - 7.06 (m, 2H), 6.66 - 6.56 (m, 3H), 3.77 - 3.69 (m, 5H), 2.40 - 2.02 (m, 5H), 1.40 (br. s., 3H), 1.40 - 1.10 (m, 5H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	0.958 A 497.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
074		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(4-(2,3-dichlorobenzyl)piperazin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.69 (d, *J*=7.9 Hz, 1H), 7.60 (d, *J*=7.3 Hz, 1H), 7.45 (t, *J*=7.8 Hz, 1H), 7.14 (t, *J*=7.7 Hz, 2H), 6.66 (t, *J*=7.1 Hz, 1H), 6.54 (d, *J*=8.1 Hz, 2H), 3.66 - 3.34 (m, 4H), 3.06 - 2.86 (m, 2H), 2.55 (s, 4H), 2.20 (br. s., 2H), 1.56 - 1.22 (m, 3H), 1.19 - 1.04 (m, 6H), 0.68 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.908 A 557.2	B
075		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(2-fluorophenyl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.48 - 7.40 (m, 1H), 7.36 - 7.28 (m, 1H), 7.22 - 7.10 (m, 4H), 6.70 - 6.62 (m, 1H), 6.55 (d, *J*=8.0 Hz, 2H), 4.02 - 3.37 (m, 5H), 2.26 (br. s., 5H), 1.41 (br. s., 3H), 1.19 - 1.07 (m, 5H), 0.71 (br. s., 3H) (2 exchangeable protons were not observed)	1.23 A 478.9	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
076		(6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (br. s., 1H), 7.88 (d, *J*=6.3 Hz, 1H), 7.44 (br. s., 1H), 7.10 (br. s., 2H), 6.73 - 6.44 (m, 3H), 3.98 - 3.34 (m, 2H), 2.55 (s, 2H), 2.34 - 2.16 (m, 3H), 2.08 (s, 1H), 1.91 (s, 2H), 1.41 (br. s., 2H), 1.15 (d, *J*=6.5 Hz, 3H), 1.09 (d, *J*=6.2 Hz, 3H), 0.72 (t, *J*=6.9 Hz, 3H) (2 exchangeable protons were not observed)	0.956 A 495.2	B
077		3-((4-bromophenyl)sulfonyl)-6-butyl-5-(ethyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, CHLOROFORM-d) δ 11.53 (s, 1H), 10.64 (br. s., 1H), 7.96 (d, *J*=8.5 Hz, 2H), 7.67 (d, *J*=8.5 Hz, 2H), 7.28 - 7.25 (m, 2H), 6.85 (t, *J*=7.3 Hz, 1H), 6.62 (d, *J*=7.7 Hz, 2H), 2.72 - 2.41 (m, 2H), 1.63 - 1.59 (m, 2H), 1.43 - 1.24 (m, 5H), 0.96 - 0.79 (m, 5H)	1.09 A 505.0	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
078		6-butyl-5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.47 (d, *J*=4.6 Hz, 1H), 8.04 (d, *J*=7.7 Hz, 2H), 7.58 (br. s., 2H), 7.27 (d, *J*=4.8 Hz, 1H), 7.09 (br. s., 2H), 6.64 - 6.55 (m, 1H), 6.51 (d, *J*=6.9 Hz, 2H), 3.17 (d, *J*=3.4 Hz, 2H), 2.24 (s, 5H), 1.44 - 1.34 (m, 2H), 1.16 (d, *J*=7.5 Hz, 2H), 1.09 (t, *J*=6.9 Hz, 3H), 0.72 (t, *J*=7.4 Hz, 3H) (2 exchangeable protons were not observed)	0.89 A 518.2	A
079		6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.47 (d, *J*=4.0 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 2H), 7.63 (d, *J*=7.2 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 2H), 7.33 (dd, *J*=7.4, 5.0 Hz, 1H), 7.06 (t, *J*=7.7 Hz, 2H), 6.55 (s, 1H), 6.47 (d, *J*=8.0 Hz, 2H), 2.41 (s, 3H), 2.32 - 2.11 (m, 2H), 1.51 - 1.34 (m, 2H), 1.22 (s, 2H), 1.19 - 1.11 (m, 2H), 1.07 (t, *J*=7.1 Hz, 3H), 0.71 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.88 A 518.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
080		6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.12 (d, *J*=4.8 Hz, 1H), 8.04 (br. s., 2H), 7.57 (br. s., 2H), 7.26 (d, *J*=4.8 Hz, 1H), 7.08 (br. s., 2H), 6.56 (d, *J*=6.1 Hz, 1H), 6.50 (br. s., 2H), 3.17 (d, *J*=4.4 Hz, 3H), 2.15 (s, 4H), 1.44 - 1.36 (m, 2H), 1.19 - 1.13 (m, 2H), 1.11 - 1.02 (m, 3H), 0.72 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.09 A 536.3	A
081		6-butyl-5-(ethyl(phenyl)amino)-3-((4-(2-methoxypyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.28 (d, *J*=5.3 Hz, 1H), 8.11 (d, *J*=8.3 Hz, 2H), 8.01 (d, *J*=8.3 Hz, 2H), 7.37 (d, *J*=4.5 Hz, 1H), 7.28 (s, 1H), 7.20 - 7.12 (m, 3H), 7.07 (s, 1H), 6.68 (t, *J*=7.2 Hz, 1H), 6.57 (d, *J*=8.2 Hz, 2H), 3.90 (s, 3H), 3.56 (br. s., 2H), 2.44 - 2.22 (m, 2H), 1.47 - 1.31 (m, 2H), 1.14 (t, *J*=7.2 Hz, 5H), 0.69 (s, 3H)	1.07 A 534.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
082		1-(4-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)phenyl)-5-chloropyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 7.98 (br. s., 3H), 7.61 (d, *J*=9.4 Hz, 3H), 7.10 (br. s., 2H), 6.68 - 6.36 (m, 4H), 3.61 (br. s., 2H), 2.40 - 2.07 (m, 2H), 1.98 - 1.63 (m, 2H), 1.37 (br. s., 2H), 1.11 (br. s., 3H), 0.69 (br. s., 3H) (2 exchangeable protons were not observed)	1.05 A 554.2	A
083		4'-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carbonitrile	^{1}H NMR (500MHz, DMSO-d_6) δ 8.01 (d, *J*=8.1 Hz, 2H), 7.96 (d, *J*=7.7 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.69 - 7.58 (m, 4H), 7.03 (t, *J*=7.7 Hz, 2H), 6.51 (s, 1H), 6.45 (d, *J*=8.0 Hz, 2H), 3.67 - 3.14 (m, 2H), 2.25 - 2.06 (m, 2H), 1.39 (d, *J*=7.1 Hz, 2H), 1.22 - 1.11 (m, 2H), 1.05 (t, *J*=7.1 Hz, 3H), 0.72 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.09 A 528.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
084		6-butyl-5-(ethyl(phenyl)amino)-3-(phenylsulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.08 - 7.72 (m, 2H), 7.53 (br. s., 3H), 7.06 (br. s., 2H), 6.69 - 6.13 (m, 3H), 3.68 - 3.01 (m, 2H), 2.38 - 1.47 (m, 4H), 1.39 - 0.96 (m, 5H), 0.68 (br. s., 3H) (2 exchangeable protons were not observed)	1.05 A 427.2	B
085		4'-((6-butyl-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (600MHz, DMSO-d_6) δ 7.90 (d, *J*=8.1 Hz, 2H), 7.74 (br. s., 1H), 7.52 - 7.41 (m, 5H), 7.39 (d, *J*=7.7 Hz, 1H), 7.31 (br. s., 1H), 7.05 (t, *J*=7.7 Hz, 2H), 6.53 (t, *J*=7.0 Hz, 1H), 6.47 (d, *J*=8.1 Hz, 2H), 3.53 (br. s., 2H), 2.25 - 2.09 (m, 2H), 1.40 (dd, *J*=13.8, 7.0 Hz, 2H), 1.20 - 1.12 (m, 2H), 1.07 (t, *J*=7.1 Hz, 3H), 0.73 (t, *J*=7.4 Hz, 3H) (2 exchangeable protons were not observed)	0.99 A 546.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
086		6-butyl-5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.97 (d, *J*=8.0 Hz, 2H), 7.83 (t, *J*=8.2 Hz, 1H), 7.50 (d, *J*=8.0 Hz, 2H), 7.13 - 6.99 (m, 3H), 6.53 (t, *J*=7.1 Hz, 1H), 6.46 (d, *J*=8.2 Hz, 2H), 2.36 (s, 3H), 2.16 (br. s., 2H), 1.39 (br. s., 2H), 1.22 (s, 2H), 1.18 - 1.09 (m, 2H), 1.06 (t, *J*=7.1 Hz, 3H), 0.71 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.10 A 536.2	A
087		6-butyl-5-(ethyl(phenyl)amino)-3-((2'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.98 (d, *J*=7.9 Hz, 2H), 7.51 (d, *J*=6.6 Hz, 3H), 7.45 - 7.38 (m, 2H), 7.30 (d, *J*=6.1 Hz, 1H), 7.08 (t, *J*=7.5 Hz, 2H), 6.58 (br. s., 1H), 6.50 (d, *J*=8.0 Hz, 2H), 4.28 (s, 2H), 3.21 (s, 3H), 2.50 - 2.49 (m, 2H), 2.20 (br. s., 2H), 1.47 - 1.34 (m, 2H), 1.16 (d, *J*=7.3 Hz, 2H), 1.09 (t, *J*=7.1 Hz, 3H), 0.72 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.13 A 547.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
088		3-([1,1'-biphenyl]-4-ylsulfonyl)-6-butyl-5-(ethyl(phenyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.99 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H), 7.71 (d, *J*=7.6 Hz, 2H), 7.50 (t, *J*=7.5 Hz, 2H), 7.43 (d, *J*=7.3 Hz, 1H), 7.07 (t, *J*=7.6 Hz, 2H), 6.60 - 6.54 (m, 1H), 6.49 (d, *J*=7.9 Hz, 2H), 3.35 - 3.24 (m, 2H), 2.31 - 2.13 (m, 2H), 1.47 - 1.32 (m, 2H), 1.20 - 1.11 (m, 2H), 1.08 (t, *J*=7.2 Hz, 3H), 0.71 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.19 A 503.2	B
090		6-butyl-5-(methyl(m-tolyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.59 - 8.42 (m, 2H), 8.05 (d, *J*=7.9 Hz, 2H), 7.59 (d, *J*=7.9 Hz, 2H), 7.27 (d, *J*=4.0 Hz, 1H), 6.99 (t, *J*=7.7 Hz, 1H), 6.45 (d, *J*=7.1 Hz, 1H), 6.37 - 6.26 (m, 2H), 3.03 (s, 3H), 2.25 (s, 5H), 2.19 (s, 3H), 1.47 - 1.36 (m, 2H), 1.24 - 1.12 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.94 A 518.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
091		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(m-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.12 (d, *J*=4.8 Hz, 1H), 8.06 (d, *J*=8.1 Hz, 2H), 7.60 (d, *J*=7.9 Hz, 2H), 7.26 (d, *J*=4.8 Hz, 1H), 6.98 (t, *J*=7.8 Hz, 1H), 6.44 (d, *J*=7.1 Hz, 1H), 6.36 - 6.28 (m, 2H), 3.02 (s, 3H), 2.22 (br. s., 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.47 - 1.36 (m, 2H), 1.24 - 1.14 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.13 A 536.2	A
092		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(p-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.02 (d, *J*=5.0 Hz, 1H), 7.96 (d, *J*=8.1 Hz, 2H), 7.50 (d, *J*=8.1 Hz, 2H), 7.16 (d, *J*=4.8 Hz, 1H), 6.82 (d, *J*=8.3 Hz, 2H), 6.31 (d, *J*=8.3 Hz, 2H), 2.91 (s, 3H), 2.19 - 2.09 (m, 2H), 2.04 (d, *J*=3.0 Hz, 6H), 1.37 - 1.24 (m, 2H), 1.13 - 1.01 (m, 2H), 0.64 (t, *J*=7.4 Hz, 3H) (2 exchangeable protons were not observed)	1.13 A 536.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
093		3-((4-bromophenyl)sulfonyl)-6-butyl-5-(methyl(m-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (400MHz, CHLOROFORM-d) δ 11.52 (br. s., 1H), 10.52 (br. s., 1H), 8.06 - 7.85 (m, 2H), 7.67 (d, *J*=8.6 Hz, 2H), 7.15 (t, *J*=7.7 Hz, 1H), 6.67 (d, *J*=7.3 Hz, 1H), 6.46 - 6.33 (m, 2H), 3.18 (s, 3H), 2.66 - 2.39 (m, 2H), 2.34 (s, 3H), 1.64 - 1.57 (m, 2H), 1.35 (dd, *J*=15.2, 7.3 Hz, 2H), 0.91 (t, *J*=7.4 Hz, 3H)	1.15 A 505.1	B
094		6-butyl-5-(methyl(p-tolyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.53 (br. s., 1H), 8.48 (d, *J*=3.2 Hz, 1H), 8.07 (d, *J*=8.1 Hz, 2H), 7.61 (d, *J*=7.9 Hz, 2H), 7.28 (d, *J*=4.6 Hz, 1H), 6.94 (d, *J*=8.3 Hz, 2H), 6.44 (d, *J*=8.1 Hz, 2H), 3.03 (s, 3H), 2.25 (s, 5H), 2.16 (s, 3H), 1.47 - 1.37 (m, 2H), 1.22 - 1.15 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.94 A 518.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
095		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(methyl(m-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (600MHz, DMSO-d_6) δ 8.06 (d, *J*=8.1 Hz, 2H), 7.86 (t, *J*=8.1 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 2H), 7.10 (d, *J*=6.9 Hz, 1H), 7.01 (t, *J*=7.8 Hz, 1H), 6.47 (d, *J*=7.3 Hz, 1H), 6.39 - 6.29 (m, 2H), 3.04 (s, 3H), 2.37 (s, 3H), 2.30 - 2.23 (m, 2H), 2.20 (s, 3H), 1.42 (d, *J*=7.7 Hz, 2H), 1.23 - 1.13 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.12 A 536.2	B
096		6-butyl-5-(methyl(m-tolyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, *J*=4.1 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 2H), 7.75 - 7.61 (m, 3H), 7.35 (dd, *J*=7.4, 4.9 Hz, 1H), 7.04 (t, *J*=7.8 Hz, 1H), 6.51 (d, *J*=7.2 Hz, 1H), 6.40 (br. s., 1H), 6.35 (d, *J*=8.0 Hz, 1H), 3.08 (s, 3H), 2.44 (s, 3H), 2.30 (d, *J*=7.9 Hz, 2H), 2.22 (s, 3H), 1.49 - 1.37 (m, 2H), 1.24 - 1.12 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.93 A 518.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
097		6-butyl-5-(methyl(p-tolyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, *J*=4.2 Hz, 1H), 8.06 (d, *J*=8.1 Hz, 2H), 7.79 - 7.56 (m, 3H), 7.35 (dd, *J*=7.4, 4.9 Hz, 1H), 6.95 (d, *J*=8.2 Hz, 2H), 6.45 (d, *J*=8.2 Hz, 2H), 3.04 (s, 3H), 2.43 (s, 3H), 2.26 (br. s., 2H), 2.17 (s, 3H), 1.42 (d, *J*=7.3 Hz, 2H), 1.24 - 1.14 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.94 A 518.2	B
098		1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(p-tolyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 8.01 (d, *J*=8.2 Hz, 2H), 7.52 - 7.45 (m, 3H), 7.41 (d, *J*=9.5 Hz, 1H), 6.88 (d, *J*=7.9 Hz, 2H), 6.45 (d, *J*=9.2 Hz, 1H), 6.37 (d, *J*=8.2 Hz, 2H), 2.96 (s, 3H), 2.14 (s, 5H), 2.05 (s, 3H), 1.40 (br. s., 2H), 1.25 - 1.14 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.09 A 534.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
099		1-(4-((6-butyl-2,4-dihydroxy-5-(methyl(m-tolyl)amino)pyridin-3-yl)sulfonyl)phenyl)-5-methylpyridin-2(1H)-one	^{1}H NMR (500MHz, DMSO-d_6) δ 8.14 (d, *J*=8.5 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 2H), 7.54 (br. s., 1H), 7.44 (dd, *J*=9.3, 2.2 Hz, 1H), 7.09 - 6.91 (m, 1H), 6.59 - 6.32 (m, 4H), 3.09 (s, 3H), 2.37 - 2.27 (m, 2H), 2.23 (s, 3H), 2.06 (s, 3H), 1.51 - 1.37 (m, 2H), 1.25 - 1.11 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.08 A 534.2	B
100		6-butyl-3-((4-cyclopropylphenyl)sulfonyl)-5-(methyl(p-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.74 (d, *J*=7.9 Hz, 2H), 7.12 (d, *J*=7.9 Hz, 2H), 6.86 (d, *J*=8.2 Hz, 2H), 6.34 (d, *J*=7.9 Hz, 2H), 2.94 (s, 3H), 2.14 (s, 5H), 2.01 - 1.87 (m, 1H), 1.43 - 1.34 (m, 2H), 1.22 - 1.12 (m, 2H), 1.00 (d, *J*=6.4 Hz, 2H), 0.80 - 0.67 (m, 5H) (2 exchangeable protons were not observed)	1.15 A 467.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
101		6-butyl-5-((3-fluorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.44 (br. s., 1H), 8.00 (d, *J*=7.6 Hz, 2H), 7.64 (d, *J*=7.6 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 2H), 7.36 - 7.28 (m, 1H), 7.09 (d, *J*=7.3 Hz, 1H), 6.38 - 6.12 (m, 3H), 2.99 (br. s., 3H), 2.39 (s, 3H), 2.19 (d, *J*=7.3 Hz, 2H), 1.38 (d, *J*=7.3 Hz, 2H), 1.24 - 1.11 (m, 2H), 0.72 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	0.91 A 522.2	A
102		6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.44 (br. s., 1H), 7.97 (d, *J*=7.9 Hz, 2H), 7.62 (d, *J*=7.0 Hz, 1H), 7.47 (d, *J*=7.6 Hz, 2H), 7.33 (br. s., 1H), 7.07 (t, *J*=7.9 Hz, 1H), 6.56 (d, *J*=7.6 Hz, 1H), 6.41 (d, *J*=7.9 Hz, 1H), 6.37 (br. s., 1H), 2.96 (s, 3H), 2.23 - 2.07 (m, 2H), 1.90 (s, 3H), 1.37 (d, *J*=7.0 Hz, 2H), 1.20 - 1.10 (m, 2H), 0.72 (t, *J*=7.0 Hz, 3H). (2 exchangeable protons were not observed)	0.99 A 538.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
103		6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.15 (d, *J*=4.9 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 2H), 7.29 (d, *J*=4.9 Hz, 1H), 7.16 (d, *J*=8.6 Hz, 2H), 6.57 (d, *J*=8.5 Hz, 2H), 3.07 (s, 3H), 2.26 (dd, *J*=17.4, 7.0 Hz, 2H), 2.16 (s, 3H), 1.53 - 1.33 (m, 2H), 1.27 - 1.13 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.20 A 556.2	A
104		6-butyl-5-((3-fluorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.58 - 8.44 (m, 2H), 8.09 (d, *J*=8.0 Hz, 2H), 7.63 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=4.6 Hz, 1H), 7.17 - 7.08 (m, 1H), 6.49 - 6.41 (m, 1H), 6.36 (d, *J*=7.4 Hz, 2H), 3.13 - 2.98 (m, 3H), 2.25 (s, 5H), 1.42 (br. s., 2H), 1.24 - 1.14 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.95 A 522.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
105		6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.08 (d, *J*=8.1 Hz, 2H), 7.88 (t, *J*=8.2 Hz, 1H), 7.64 (d, *J*=8.1 Hz, 2H), 7.19 - 7.09 (m, 2H), 6.70 (d, *J*=7.6 Hz, 1H), 6.58 (br. s., 1H), 6.51 (d, *J*=8.2 Hz, 1H), 3.08 (s, 3H), 2.38 (s, 3H), 2.33 - 2.21 (m, 2H), 1.42 (dt, *J*=15.0, 7.6 Hz, 2H), 1.24 - 1.12 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.14 A 556.1	B
106		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((3-fluorophenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 - 8.09 (m, 3H), 7.67 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=4.9 Hz, 1H), 7.15 (d, *J*=7.8 Hz, 1H), 6.49 - 6.43 (m, 1H), 6.37 (d, *J*=9.2 Hz, 2H), 3.08 (s, 3H), 2.27 (dd, *J*=16.7, 6.6 Hz, 2H), 2.16 (s, 3H), 1.54 - 1.34 (m, 2H), 1.24 - 1.07 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.12 A 540.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
107		6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.18 - 8.08 (m, 3H), 7.66 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=4.9 Hz, 1H), 7.15 (t, *J*=8.1 Hz, 1H), 6.69 (d, *J*=7.6 Hz, 1H), 6.58 (br. s., 1H), 6.51 (d, *J*=7.6 Hz, 1H), 3.08 (s, 3H), 2.27 (dd, *J*=19.2, 6.4 Hz, 2H), 2.16 (s, 3H), 1.54 - 1.32 (m, 2H), 1.26 - 1.13 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.19 A 556.2	A
108		6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.58 - 8.42 (m, 2H), 8.08 (d, *J*=7.7 Hz, 2H), 7.63 (d, *J*=7.6 Hz, 2H), 7.28 (br. s., 1H), 7.15 (d, *J*=8.2 Hz, 2H), 6.56 (d, *J*=8.4 Hz, 2H), 3.27 - 2.93 (m, 3H), 2.24 (br. s., 5H), 1.41 (br. s., 2H), 1.25 - 1.10 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.01 A 538.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
109		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((3-fluorophenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.09 (d, *J*=8.2 Hz, 2H), 7.88 (s, 1H), 7.64 (d, *J*=7.9 Hz, 2H), 7.14 (dd, *J*=15.6, 7.9 Hz, 2H), 6.46 (br. s., 1H), 6.38 (d, *J*=9.2 Hz, 2H), 3.09 (s, 3H), 2.39 (s, 3H), 2.29 (dd, *J*=16.8, 9.5 Hz, 2H), 1.52 - 1.37 (m, 2H), 1.27 - 1.14 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.11 A 540.2	B
110		6-butyl-5-((3-chlorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.77 - 8.61 (m, 2H), 8.17 (d, *J*=8.2 Hz, 2H), 7.74 (d, *J*=8.2 Hz, 2H), 7.58 (d, *J*=4.6 Hz, 1H), 7.22 - 7.11 (m, 1H), 6.73 (d, *J*=7.7 Hz, 1H), 6.63 (br. s., 1H), 6.54 (d, *J*=7.8 Hz, 1H), 3.12 (s, 3H), 2.32 (s, 5H), 1.57 - 1.33 (m, 2H), 1.26 - 1.14 (m, 2H), 0.75 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.01 A 538.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
111		6-butyl-5-((4-chlorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.69 (d, *J*=4.3 Hz, 1H), 8.15 (d, *J*=8.1 Hz, 2H), 8.07 (d, *J*=7.7 Hz, 1H), 7.73 (d, *J*=8.1 Hz, 2H), 7.68 (d, *J*=6.4 Hz, 1H), 7.20 (d, *J*=8.7 Hz, 2H), 6.62 (d, *J*=8.7 Hz, 2H), 3.11 (s, 3H), 2.51 - 2.48 (m, 3H), 2.44 - 2.23 (m, 2H), 1.42 (dd, *J*=15.6, 8.7 Hz, 2H), 1.27 - 1.13 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	0.99 A 538.2	A
112		6-butyl-5-((2-fluorophenyl)(methyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.61 - 8.42 (m, 2H), 7.99 (d, *J*=7.9 Hz, 2H), 7.51 (d, *J*=7.9 Hz, 2H), 7.25 (d, *J*=4.9 Hz, 1H), 6.89 (d, *J*=7.6 Hz, 2H), 6.63 (d, *J*=7.6 Hz, 2H), 3.05 (br. s., 3H), 2.30 - 2.19 (m, 5H), 1.48 - 1.22 (m, 2H), 1.19 - 1.10 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.96 A 522.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
113		3-((2-butyl-4,6-dihydroxy-5-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridin-3-yl)(methyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.46 (d, *J*=4.6 Hz, 1H), 7.97 (d, *J*=7.9 Hz, 2H), 7.50 (d, *J*=7.9 Hz, 2H), 7.25 (d, *J*=4.6 Hz, 2H), 6.95 (d, *J*=7.3 Hz, 1H), 6.77 (br. s., 2H), 3.01 (s, 3H), 2.24 (s, 3H), 2.21 - 2.07 (m, 2H), 1.40 (d, *J*=7.9 Hz, 2H), 1.23 - 1.14 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.81 A 529.0	A
114		5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.13 (d, *J*=8.2 Hz, 2H), 7.89 (t, *J*=8.1 Hz, 1H), 7.68 (d, *J*=8.2 Hz, 2H), 7.26 - 7.07 (m, 7H), 6.68 (t, *J*=7.2 Hz, 1H), 6.61 (d, *J*=7.9 Hz, 2H), 3.30 - 3.02 (m, 2H), 2.40 (s, 3H), 2.19 (s, 3H), 0.83 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.10 A 570.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
115		6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.11 (d, *J*=8.0 Hz, 2H), 7.89 (t, *J*=8.2 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 2H), 7.13 (d, *J*=6.1 Hz, 1H), 6.83 (d, *J*=7.7 Hz, 1H), 6.80 - 6.75 (m, 1H), 6.70 - 6.65 (m, 1H), 6.37 (d, *J*=7.9 Hz, 1H), 4.37 - 4.04 (m, 2H), 3.94 - 3.34 (m, 2H), 2.46 - 2.28 (m, 5H), 1.99 (br. s., 2H), 1.44 - 1.24 (m, 2H), 1.20 - 1.12 (m, 2H), 0.72 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.02 A 564.2	B
116		6-butyl-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.65 - 8.45 (m, 2H), 7.88 (d, *J*=8.0 Hz, 2H), 7.67 (d, *J*=8.0 Hz, 2H), 7.36 - 7.17 (m, 5H), 7.15 - 6.99 (m, 1H), 4.33 (d, *J*=10.8 Hz, 1H), 3.09 - 2.90 (m, 2H), 2.26 (s, 3H), 2.15 - 1.86 (m, 2H), 1.80 - 1.61 (m, 4H), 1.47 - 1.39 (m, 2H), 1.36 - 1.29 (m, 2H), 1.16 (t, *J*=7.2 Hz, 2H), 0.93 (t, *J*=7.1 Hz, 3H) (2 exchangeable protons were not observed)	0.97 A 558.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
117		3-((2-butyl-5-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(methyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d_6) δ 7.92 (d, *J*=8.1 Hz, 2H), 7.82 (t, *J*=8.2 Hz, 1H), 7.45 (d, *J*=8.0 Hz, 2H), 7.22 (t, *J*=8.0 Hz, 1H), 7.09 (d, *J*=8.2 Hz, 1H), 6.92 (d, *J*=7.3 Hz, 1H), 6.76 - 6.70 (m, 2H), 2.98 (s, 3H), 2.36 (s, 3H), 2.21 - 2.03 (m, 2H), 1.38 (d, *J*=7.2 Hz, 2H), 1.22 - 1.13 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.03 A 547.0	A
118		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-((2-fluorophenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.08 (d, *J*=7.9 Hz, 2H), 7.89 (t, *J*=8.1 Hz, 1H), 7.66 (d, *J*=7.9 Hz, 2H), 7.15 - 7.10 (m, 1H), 7.07 - 6.98 (m, 2H), 6.91 (t, *J*=8.9 Hz, 1H), 6.78 (d, *J*=4.0 Hz, 1H), 3.13 (s, 3H), 2.39 (s, 3H), 2.37 - 2.32 (m, 2H), 1.49 - 1.20 (m, 2H), 1.19 - 1.06 (m, 2H), 0.72 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.07 A 540.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
119		3-((2-butyl-4,6-dihydroxy-5-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridin-3-yl)(methyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d_6) δ 8.49 (d, *J*=4.0 Hz, 1H), 7.98 (d, *J*=7.9 Hz, 2H), 7.63 (d, *J*=7.3 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 2H), 7.35 - 7.31 (m, 1H), 7.26 (t, *J*=7.8 Hz, 1H), 6.97 (d, *J*=7.3 Hz, 1H), 6.80 (d, *J*=14.3 Hz, 2H), 3.03 (s, 3H), 2.42 (s, 3H), 2.27 - 2.09 (m, 2H), 1.41 (d, *J*=5.5 Hz, 2H), 1.25 - 1.14 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.80 A 529.0	A
120		5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.61 - 8.46 (m, 2H), 8.14 (d, *J*=8.2 Hz, 2H), 7.69 (d, *J*=7.9 Hz, 2H), 7.30 (d, *J*=4.9 Hz, 1H), 7.19 (dd, *J*=18.8, 10.5 Hz, 5H), 7.09 (d, *J*=7.3 Hz, 1H), 6.68 (t, *J*=6.9 Hz, 1H), 6.61 (d, *J*=7.9 Hz, 2H), 3.28 - 3.02 (m, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 0.83 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	0.84 A 552.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
122		5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(m-tolyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 (d, *J*=6.1 Hz, 3H), 7.70 (d, *J*=7.9 Hz, 2H), 7.31 (d, *J*=4.6 Hz, 1H), 7.25 - 7.15 (m, 5H), 7.10 (d, *J*=7.3 Hz, 1H), 6.67 (t, *J*=7.0 Hz, 1H), 6.62 (d, *J*=7.9 Hz, 2H), 3.30 - 3.05 (m, 2H), 2.19 (d, *J*=6.7 Hz, 6H), 0.83 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	1.10 A 570.3	A
123		6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, *J*=4.6 Hz, 1H), 8.10 (d, *J*=7.9 Hz, 2H), 7.73 - 7.58 (m, 3H), 7.39 - 7.28 (m, 1H), 6.83 (d, *J*=7.6 Hz, 1H), 6.77 (s, 1H), 6.69 - 6.63 (m, 1H), 6.36 (d, *J*=7.9 Hz, 1H), 4.37 - 4.04 (m, 2H), 3.73 - 3.43 (m, 2H), 2.44 (s, 3H), 2.37 - 2.26 (m, 2H), 2.05 - 1.91 (m, 2H), 1.42 - 1.23 (m, 2H), 1.20 - 1.13 (m, 2H), 0.73 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.88 A 546.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
124		6-butyl-5-((2-fluorophenyl)(methyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, *J*=3.7 Hz, 1H), 8.01 (d, *J*=8.2 Hz, 2H), 7.65 (d, *J*=7.3 Hz, 1H), 7.56 (d, *J*=7.9 Hz, 2H), 7.38 - 7.30 (m, 1H), 7.01 - 6.91 (m, 2H), 6.78 - 6.65 (m, 2H), 3.08 (s, 3H), 2.44 (s, 3H), 2.27 (br. s., 2H), 1.47 - 1.23 (m, 2H), 1.20 - 1.11 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.88 A 522.3	A
125		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-((2-fluorophenyl)(methyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.14 (d, *J*=4.9 Hz, 1H), 8.09 (d, *J*=7.9 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 2H), 7.29 (d, *J*=4.9 Hz, 1H), 7.05 - 6.97 (m, 2H), 6.85 (br. s., 1H), 6.75 (br. s., 1H), 3.11 (s, 3H), 2.31 (br. s., 2H), 2.16 (s, 3H), 1.23 (br. s., 2H), 1.15 (d, *J*=5.2 Hz, 2H), 0.72 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.11 A 540.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
126		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 7.92 - 7.83 (m, 3H), 7.66 (d, *J*=7.9 Hz, 2H), 7.27 - 7.24 (m, 2H), 7.21 (t, *J*=7.3 Hz, 2H), 7.16 - 7.09 (m, 2H), 4.33 (d, *J*=10.7 Hz, 1H), 3.51 - 3.16 (m, 2H), 3.08 - 2.84 (m, 2H), 2.39 (s, 3H), 1.92 - 1.59 (m, 5H), 1.51 - 1.30 (m, 5H), 0.93 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	1.18 A 576.3	B
127		6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.14 (d, *J*=4.9 Hz, 1H), 8.08 (d, *J*=7.9 Hz, 2H), 7.60 (d, *J*=7.6 Hz, 2H), 7.28 (d, *J*=4.9 Hz, 1H), 6.78 (d, *J*=7.6 Hz, 1H), 6.74 - 6.67 (m, 1H), 6.61 (d, *J*=7.0 Hz, 1H), 6.31 (d, *J*=7.9 Hz, 1H), 4.36 - 4.03 (m, 2H), 3.68 (d, *J*=10.1 Hz, 1H), 2.89 (d, *J*=7.3 Hz, 1H), 2.40 - 2.24 (m, 2H), 2.17 (s, 3H), 2.05 - 1.88 (m, 2H), 1.44 - 1.25 (m, 2H), 1.21 - 1.12 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.08 A 564.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
128		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-phenylpiperidin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.15 (d, *J*=4.6 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 2H), 7.66 (d, *J*=7.9 Hz, 2H), 7.30 - 7.15 (m, 5H), 7.11 (d, *J*=6.7 Hz, 1H), 4.34 (d, *J*=10.7 Hz, 1H), 3.54 (br. s., 2H), 3.06 - 2.78 (m, 2H), 2.16 (s, 3H), 1.90 - 1.58 (m, 5H), 1.50 - 1.28 (m, 5H), 0.92 (t, *J*=6.9 Hz, 3H) (2 exchangeable protons were not observed)	1.18 A 576.3	B
129		6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.65 - 8.39 (m, 2H), 8.00 (d, *J*=7.6 Hz, 2H), 7.50 (d, *J*=7.6 Hz, 2H), 7.26 (br. s., 1H), 6.77 - 6.69 (m, 1H), 6.65 - 6.60 (m, 1H), 6.53 (s, 1H), 6.24 (d, *J*=7.9 Hz, 1H), 4.37 - 4.05 (m, 2H), 3.72 - 3.20 (m, 2H), 2.25 (s, 5H), 1.91 (s, 2H), 1.32 (d, *J*=7.0 Hz, 2H), 1.22 - 1.10 (m, 2H), 0.73 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.85 A 546.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
130		(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (br. s., 1H), 7.94 (d, *J*=11.0 Hz, 1H), 7.24 - 7.01 (m, 7H), 6.67 (br. s., 1H), 6.56 (d, *J*=7.5 Hz, 1H), 3.94 - 3.37 (m, 4H), 3.27 - 2.90 (m, 2H), 2.18 (br. s., 6H), 0.79 (br. s., 3H) (2 exchangeable protons were not observed)	0.95 A 531.3	A
131		3-((4-bromophenyl)sulfonyl)-5-(ethyl(phenyl)amino)-6-(m-tolyl)pyridine-2,4-diol	^{1}H NMR (400MHz, CHLOROFORM-d) δ 11.76 - 11.43 (m, 1H), 10.56 - 10.17 (m, 1H), 7.75 (d, *J*=8.4 Hz, 2H), 7.49 (d, *J*=8.4 Hz, 2H), 7.35 - 7.30 (m, 4H), 7.25 (s, 2H), 6.92 - 6.82 (m, 1H), 6.68 (d, *J*=7.9 Hz, 2H), 3.44 - 3.12 (m, 2H), 2.37 (s, 3H), 0.94 (t, *J*=7.2 Hz, 3H)	1.26 A 539.2	B
132		(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.62 - 8.42 (m, 1H), 8.06 - 7.85 (m, 1H), 7.27 - 6.99 (m, 6H), 6.75 - 6.44 (m, 3H), 3.38 (br. s., 1H), 3.18 (d, *J*=4.3 Hz, 3H), 3.02 - 2.84 (m, 1H), 2.19 (br. s., 4H), 1.92 (s, 1H), 1.29 - 1.11 (m, 2H), 0.78 (br. s., 3H) (2 exchangeable protons were not observed)	1.03 A 531.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
133		6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.58 - 8.46 (m, 2H), 8.08 (d, *J*=8.2 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 2H), 7.28 (br. s., 1H), 6.31 (br. s., 1H), 6.16 (s, 2H), 2.50 - 2.48 (m, 2H), 2.25 (s, 5H), 2.15 (s, 6H), 1.48 - 1.36 (m, 2H), 1.20 - 1.14 (m, 2H), 1.11 (t, *J*=6.9 Hz, 3H), 0.73 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.99 A 546.3	A
134		3-((4-bromophenyl)sulfonyl)-6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)pyridine-2,4-diol	^{1}H NMR (400MHz, CHLOROFORM-d) δ 11.55 (br. s., 1H), 10.74 (br. s., 1H), 7.94 (d, *J*=8.8 Hz, 2H), 7.67 (d, *J*=8.6 Hz, 2H), 6.49 (s, 1H), 6.22 (s, 2H), 3.70 - 3.45 (m, 2H), 2.55 (t, *J*=8.0 Hz, 2H), 2.28 (s, 6H), 1.68 - 1.58 (m, 2H), 1.41 - 1.31 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 0.91 (t, *J*=7.3 Hz, 3H)	1.21 A 533.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
135		6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.02 (d, *J*=7.7 Hz, 2H), 7.90 - 7.78 (m, 1H), 7.58 (d, *J*=7.1 Hz, 2H), 7.10 (d, *J*=7.8 Hz, 1H), 6.26 (br. s., 1H), 6.12 (br. s., 2H), 3.16 (br. s., 2H), 2.37 (s, 3H), 2.31 - 2.19 (m, 2H), 2.13 (s, 6H), 1.40 (br. s., 2H), 1.19 - 1.12 (m, 2H), 1.07 (t, *J*=6.9 Hz, 3H), 0.72 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	1.18 A 564.3	A
136		6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d_6) δ 8.12 (d, *J*=4.5 Hz, 1H), 8.07 (d, *J*=7.7 Hz, 2H), 7.63 (d, *J*=7.3 Hz, 2H), 7.27 (d, *J*=4.3 Hz, 1H), 6.28 (br. s., 1H), 6.13 (br. s., 2H), 3.57 - 3.19 (m, 2H), 2.40 - 2.20 (m, 2H), 2.17 - 2.09 (m, 9H), 1.39 (d, *J*=7.6 Hz, 2H), 1.19 - 1.12 (m, 2H), 1.08 (t, *J*=6.9 Hz, 3H), 0.72 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.16 A 564.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
137		4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.15 (d, *J*=4.6 Hz, 1H), 7.95 (d, *J*=7.9 Hz, 2H), 7.54 - 7.47 (m, 3H), 7.45 - 7.38 (m, 3H), 7.30 (t, *J*=7.9 Hz, 1H), 7.02 (d, *J*=7.3 Hz, 1H), 6.89 - 6.80 (m, 2H), 3.05 (s, 3H), 2.58 (d, *J*=4.6 Hz, 3H), 2.32 - 2.14 (m, 2H), 1.39 (dd, *J*=16.3, 7.2 Hz, 2H), 1.19 - 1.11 (m, 2H), 0.72 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.14 A 571.2	A
138		4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.94 (br. s., 1H), 7.73 (br. s., 1H), 7.53 - 7.35 (m, 5H), 7.30 (br. s., 1H), 7.24 (br. s., 1H), 6.93 (br. s., 1H), 6.74 (br. s., 2H), 3.47 (br. s., 2H), 2.98 (br. s., 2H), 1.92 (br. s., 2H), 1.23 (s, 5H), 0.74 (br. s., 3H) (2 exchangeable protons were not observed)	1.07 A 557.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
139		4'-((6-butyl-5-((3-cyanophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.96 (d, *J*=7.0 Hz, 2H), 7.61 - 7.46 (m, 5H), 7.36 (d, *J*=7.2 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.01 (d, *J*=7.2 Hz, 1H), 6.92 - 6.77 (m, 2H), 2.55 (s, 6H), 2.49 (br. s., 3H), 2.33 - 2.13 (m, 2H), 1.46 - 1.34 (m, 2H), 1.21 - 1.14 (m, 2H), 0.75 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.11 A 585.3	A
140		4'-((6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.91 (d, *J*=7.9 Hz, 2H), 7.56 - 7.42 (m, 5H), 7.35 (d, *J*=7.3 Hz, 1H), 6.19 (br. s., 1H), 6.08 (s, 2H), 2.75 (s, 2H), 2.55 (s, 6H), 2.11 (s, 8H), 1.41 (br. s., 2H), 1.20 - 1.12 (m, 2H), 1.04 (t, *J*=7.0 Hz, 3H), 0.74 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.25 A 602.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
141		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.93 (d, *J*=8.0 Hz, 2H), 7.56 - 7.33 (m, 6H), 7.11 (br. s., 3H), 7.07 - 7.00 (m, 3H), 6.55 - 6.45 (m, 3H), 3.05 (d, *J*=6.6 Hz, 2H), 2.76 (s, 3H), 2.45 (br. s., 3H), 2.17 (s, 3H), 0.71 (t, *J*=7.1 Hz, 3H) (2 exchangeable protons were not observed)	1.21 A 608.4	A
142		4'-((6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 7.91 (d, *J*=8.1 Hz, 2H), 7.52 (d, *J*=7.5 Hz, 1H), 7.47 (d, *J*=3.3 Hz, 2H), 7.41 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=7.5 Hz, 1H), 6.71 (d, *J*=7.6 Hz, 1H), 6.65 - 6.59 (m, 1H), 6.52 (t, *J*=7.4 Hz, 1H), 6.22 (d, *J*=7.9 Hz, 1H), 4.30 - 4.03 (m, 2H), 3.73 - 3.56 (m, 2H), 2.31 - 2.14 (m, 2H), 1.98 - 1.79 (m, 8H), 1.37 - 1.25 (m, 2H), 1.18 - 1.07 (m, 2H), 0.72 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.14 A 602.2	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
143		4'-((6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	)+. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=7.6 Hz, 2H), 7.73 (br. s., 1H), 7.47 (d, *J*=11.3 Hz, 5H), 7.38 (d, *J*=7.3 Hz, 1H), 7.30 (br. s., 1H), 6.18 (br. s., 1H), 6.08 (br. s., 2H), 3.32 - 3.14 (m, 2H), 2.21 - 2.05 (m, 8H), 1.41 (br. s., 2H), 1.16 (d, *J*=7.3 Hz, 2H), 1.05 (t, *J*=7.0 Hz, 3H), 0.74 (t, *J*=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.15 A 574.3	A
144		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.02 (d, *J*=7.9 Hz, 2H), 7.82 (br. s., 1H), 7.61 - 7.44 (m, 4H), 7.42 (d, *J*=7.6 Hz, 1H), 7.35 (br. s., 1H), 7.20 - 7.12 (m, 4H), 7.08 (d, *J*=6.7 Hz, 1H), 6.63 (br. s., 1H), 6.57 (d, *J*=7.3 Hz, 2H), 3.22 - 3.03 (m, 2H), 2.18 (s, 3H), 1.29 - 1.20 (m, 2H), 0.79 (t, *J*=6.9 Hz, 3H) (2 exchangeable protons were not observed)	1.13 A 580.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
145		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(m-tolyl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.12 (d, *J*=4.0 Hz, 1H), 7.95 - 7.89 (m, 2H), 7.51 (d, *J*=6.7 Hz, 1H), 7.45 - 7.39 (m, 5H), 7.11 (br. s., 3H), 7.08 - 7.02 (m, 3H), 6.52 (t, *J*=6.9 Hz, 1H), 6.47 (d, *J*=7.9 Hz, 2H), 3.07 (d, *J*=6.7 Hz, 2H), 2.59 (d, *J*=4.0 Hz, 3H), 2.17 (s, 3H), 0.72 (t, *J*=7.0 Hz, 3H) (2 exchangeable protons were not observed)	1.18 A 594.3	A
146		4'-((6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d_6) δ 8.12 (br. s., 1H), 7.96 - 7.90 (m, 2H), 7.51 (d, *J*=5.2 Hz, 1H), 7.44 (d, *J*=6.4 Hz, 5H), 6.73 (d, *J*=7.3 Hz, 1H), 6.69 - 6.62 (m, 1H), 6.54 (br. s., 1H), 6.27 (d, *J*=7.9 Hz, 1H), 4.32 - 4.07 (m, 2H), 3.70 (br. s., 2H), 2.59 (d, *J*=4.3 Hz, 3H), 2.33 - 2.16 (m, 2H), 1.92 (s, 2H), 1.41 - 1.27 (m, 2H), 1.21 - 1.13 (m, 2H), 0.74 (t, *J*=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.11 A 588.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
147		4'-((6-(cyclopropylmethyl)-5-(ethyl(phenyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.82 (d, J=7.6 Hz, 2H), 7.63 (br. s., 1H), 7.43 - 7.25 (m, 6H), 7.20 (br. s., 1H), 6.95 (t, J=7.5 Hz, 2H), 6.48 - 6.42 (m, 1H), 6.39 (d, J=7.9 Hz, 2H), 3.33 - 3.20 (m, J=7.6 Hz, 2H), 2.03 (dd, J=18.5, 6.6 Hz, 2H), 0.96 (t, J=7.0 Hz, 3H), 0.74 (d, J=16.8 Hz, 1H), 0.27 - 0.13 (m, 2H), 0.04 - -0.04 (m, 1H), -0.08 - -0.16 (m, 1H) (2 exchangeable protons not observed)	1.15 A 544.3	A
148		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.06 (d, J=7.9 Hz, 2H), 7.95 (s, 1H), 7.85 (br. s., 1H), 7.74 (br. s., 1H), 7.64 (d, J=7.7 Hz, 2H), 7.57 - 7.37 (m, 4H), 7.17 (d, J=7.3 Hz, 2H), 6.72 - 6.61 (m, 3H), 6.31 (br. s., 1H), 3.47 - 3.39 (m, 2H), 2.89 (s, 3H), 1.03 (t, J=6.7 Hz, 3H) (4 exchangeable protons not observed)	1.10 A 570.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
149		5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)sulfonyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.13 (d, J=4.9 Hz, 1H), 8.11 - 8.05 (m, 3H), 7.70 (s, 1H), 7.62 (d, J=7.6 Hz, 2H), 7.27 (d, J=4.9 Hz, 1H), 7.13 (t, J=7.5 Hz, 2H), 6.68 - 6.57 (m, 3H), 3.78 (s, 3H), 3.44 (m, 2H), 2.15 (s, 3H), 0.98 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.11 A 560.4	A
150		5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-4-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.51 (d, J=4.0 Hz, 1H), 8.14 - 8.05 (m, 3H), 7.74 (s, 1H), 7.71 - 7.61 (m, 3H), 7.39 - 7.32 (m, 1H), 7.18 (t, J=7.6 Hz, 2H), 6.70 (t, J=7.2 Hz, 1H), 6.65 (d, J=7.9 Hz, 2H), 3.78 (s, 3H), 3.56 - 3.40 (m, 2H), 2.43 (s, 3H), 1.02 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	0.83 A 542.3	A
151		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.18 (br. s., 1H), 8.12 (s, 1H), 8.01 (d, J=7.6 Hz, 2H), 7.72 (s, 1H), 7.57 - 7.51 (m, 3H), 7.49 - 7.41 (m, 3H), 7.15 (t, J=7.3 Hz, 2H), 6.70 - 6.60 (m, 3H), 3.79 (s, 3H), 3.56 - 3.36 (m, 2H), 2.59 (d, J=4.3 Hz, 3H), 1.00 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.02 A 584.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
152		5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.15 (br. s., 1H), 8.07 (d, J=7.3 Hz, 2H), 7.87 (t, J=7.8 Hz, 1H), 7.71 (br. s., 1H), 7.60 (d, J=6.1 Hz, 2H), 7.19 - 7.07 (m, 3H), 6.68 - 6.59 (m, 3H), 3.80 (s, 3H), 3.52 - 3.36 (m, 2H), 2.38 (s, 3H), 0.99 (t, J=6.6 Hz, 3H) (2 exchangeable protons not observed)	1.13 A 560.3	A
153		N-cyclopropyl-4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.98 (br. s., 1H), 7.92 (d, J=3.7 Hz, 1H), 7.66 (d, J=7.9 Hz, 2H), 7.35 (s, 1H), 7.24 (t, J=7.3 Hz, 1H), 7.20 - 7.09 (m, 5H), 6.81 (t, J=7.6 Hz, 2H), 6.32 - 6.25 (m, 3H), 3.54 (s, 3H), 3.27 - 3.05 (m, 4H), 0.67 (t, J=7.2 Hz, 3H), 0.26 (d, J=5.8 Hz, 2H), 0.01 (br. s., 2H) (1 exchangeable proton not observed)	1.84 A 610.0	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
154		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.17 (br. s., 1H), 7.98 (d, J=6.7 Hz, 2H), 7.67 (br. s., 1H), 7.56 - 7.44 (m, 5H), 7.35 (d, J=7.3 Hz, 1H), 7.10 (br. s., 2H), 6.58 (d, J=7.9 Hz, 3H), 3.78 (s, 3H), 3.47 - 3.34 (m, 3H), 2.74 (s, 3H), 2.45 (br. s., 3H), 0.95 (t, J=6.7 Hz, 3H) (1 exchangeable proton not observed)	1.86 A 598.1	A
155		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)sulfonyl)-4-fluoro-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.09 (br. s., 1H), 7.94 (br. s., 2H), 7.86 (br. s., 1H), 7.66 (br. s., 1H), 7.50 (br. s., 2H), 7.44 (br. s., 2H), 7.39 - 7.25 (m, 2H), 7.11 (br. s., 2H), 6.59 (br. s., 3H), 3.77 (s, 3H), 3.55 - 3.41 (m, 2H), 1.02 - 0.89 (m, 3H) (2 exchangeable protons not observed)	1.04 A 588.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
156		5-(ethyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-4-yl)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.52 (s, 1H), 8.46 (d, J=4.9 Hz, 1H), 8.03 (s, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.61 (s, 1H), 7.47 (d, J=8.2 Hz, 2H), 7.24 (d, J=4.9 Hz, 1H), 7.04 (t, J=7.6 Hz, 2H), 6.56 - 6.48 (m, 3H), 3.76 (s, 3H), 3.40 - 3.23 (m, 2H), 2.24 (s, 3H), 0.90 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	0.89 A 542.3	A
157		3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.13 (d, J=8.2 Hz, 2H), 7.90 (t, J=7.9 Hz, 1H), 7.70 (d, J=9.8 Hz, 2H), 7.28 - 7.04 (m, 4H), 6.67 (d, J=7.6 Hz, 3H), 6.25 (br. s., 1H), 3.87 (s, 3H), 2.40 (s, 3H), 1.29 - 1.13 (m, 4H), 0.92 (d, J=6.1 Hz, 3H) (2 exchangeable protons not observed)	2.24 A 574.2	A
158		4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.21 - 8.14 (m, 1H), 8.01 (m, 2H), 7.68 (m, 1H), 7.54 (m, 3H), 7.46 (m, 3H), 7.14 (m, 2H), 6.64 (m, 3H), 6.24 (m, 1H), 4.15 (m, 1H), 3.44 (m, 3H), 2.59 (m, 3H), 1.18 (m, 3H), 0.93 (m, 3H) (2 exchangeable protons not observed)	1.93 A 598.1	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
159		4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.99 - 7.86 (m, 2H), 7.61 (br. s., 1H), 7.56 - 7.37 (m, 5H), 7.33 (m, 1H), 7.02 (m, 2H), 6.59 - 6.46 (m, 3H), 6.18 (m, 1H), 3.82 (m, 3H), 3.56 (m, 3H), 2.71 (m, 3H), 1.06 (m, 3H), 0.88 (m, 3H) (2 exchangeable protons not observed)	2.08 A 612.3	A
160		5-(3,3-dimethylindolin-1-yl)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.25 - 7.99 (m, 3H), 7.73 (m, 1H), 7.67 - 7.49 (m, 2H), 7.27 (m, 1H), 7.02 (m, 1H), 6.83 (m, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 5.97 (m, 1H), 3.88 (m, 2H), 3.39 (m, 3H), 2.15 (m, 3H), 1.37 (m, 3H), 1.24 (m, 3H) (2 exchangeable protons not observed)	1.28 A 586.4	B
161		4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-4-fluoro-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.03 (d, J=7.3 Hz, 2H), 7.90 (m, 1H), 7.69 (m, 1H), 7.59 (m, 2H), 7.48 (m, 2H), 7.41 - 7.31 (m, 2H), 7.15 (m, 2H), 6.64 (m, 3H), 6.24 (br. s., 1H), 4.16 (m, 1H), 3.86 (s, 3H), 1.18 (d, J=4.3 Hz, 3H), 0.92 (d, J=5.8 Hz, 3H) (2 exchangeable protons not observed)	1.94 A 602.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
162		N-cyclopropyl-4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.00 (m, 1H), 7.81 (m, 2H), 7.45 (m, 1H), 7.37 - 7.20 (m, 6H), 6.93 (m, 2H), 6.43 (m, 3H), 6.04 (m, 1H), 3.94 (m, 1H), 3.60 (br. s., 3H), 2.29 (m, 1H), 0.97 (br. s., 3H), 0.74 (br. s., 3H), 0.31 (d, J=5.8 Hz, 2H), 0.00 (br. s., 2H) (2 exchangeable protons not observed)	2.05 A 624.2	A
163		4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.60 (m, 1H), 8.19 - 8.01 (m, 3H), 7.97 - 7.79 (m, 4H), 7.68 - 7.56 (m, 2H), 7.11 (m, 2H), 6.61 (m, 2H), 6.21 (br. s., 1H), 4.12 (m, 1H), 3.58 (br. s., 3H), 2.81 (d, J=4.3 Hz, 3H), 1.14 (br. s., 3H), 0.90 (br. s., 3H) (3 exchangeable protons not observed)	2.04 A 598.1	A
164		3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.11 (m 1H), 7.98 (m, 2H), 7.62 (m, 1H), 7.47 (m, 2H), 7.37 - 7.12 (m, 2H), 7.01 (m, 2H), 6.50 (m, 2H), 6.17 (m, 1H), 4.01 (m, 1H), 3.83 (br. s., 3H), 2.12 (br. s., 3H), 1.03 (br. s., 3H), 0.87 (br. s., 3H) (2 exchangeable protons not observed)	1.27 A 574.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
165		5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.47 (d, J=3.7 Hz, 1H), 7.94 (d, J=6.4 Hz, 1H), 7.65 - 7.57 (m, 2H), 7.44 (d, J=7.0 Hz, 2H), 7.35 - 7.27 (m, 1H), 7.06 - 6.96 (m, 2H), 6.57 - 6.43 (m, 3H), 6.16 (br. s., 1H), 4.07 - 3.97 (m, 1H), 3.35 (br. s., 3H), 2.41 (br. s., 3H), 1.06 (d, J=4.9 Hz, 3H), 0.89 (d, J=4.6 Hz, 3H) (2 exchangeable protons not observed)	1.00 A 556.4	A
166		4'-((2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.09 - 7.96 (m, 2H), 7.85 - 7.76 (m, 1H), 7.72 - 7.63 (m, 1H), 7.61 - 7.38 (m, 5H), 7.34 (br. s., 1H), 7.26 (br. s., 1H), 7.19 - 7.03 (m, 3H), 6.70 - 6.55 (m, 2H), 6.25 - 6.15 (m, 1H), 4.20 - 4.09 (m, 1H), 3.35 (br. s., 3H), 1.28 (br. s., 3H), 0.98 - 0.82 (m, 3H) (2 exchangeable protons not observed)	1.24 A 585.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
167-I		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, CHLOROFORM-d) δ 8.20 (d, J=8.0 Hz, 2H), 8.12 (d, J=4.7 Hz, 1H), 7.50 (d, J=7.7 Hz, 2H), 7.12 - 7.03 (m, 2H), 7.01 - 6.94 (m, 1H), 6.75 - 6.68 (m, 1H), 6.16 (d, J=8.0 Hz, 1H), 3.84 - 3.56 (m, 1H), 3.06 - 2.80 (m, 2H), 2.69 - 2.46 (m, 2H), 2.22 (s, 3H), 2.18 - 1.86 (m, 2H), 1.48 - 1.32 (m, 4H), 1.26 - 1.08 (m, 3H), 0.95 - 0.84 (m, 3H) (2 exchangeable protons not observed)	1.29 A 562.4	A
167-II		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, CHLOROFORM-d) δ 8.20 (d, J=8.0 Hz, 2H), 8.12 (d, J=4.7 Hz, 1H), 7.50 (d, J=7.7 Hz, 2H), 7.12 - 7.03 (m, 2H), 7.01 - 6.94 (m, 1H), 6.75 - 6.68 (m, 1H), 6.16 (d, J=8.0 Hz, 1H), 3.84 - 3.56 (m, 1H), 3.06 - 2.80 (m, 2H), 2.69 - 2.46 (m, 2H), 2.22 (s, 3H), 2.18 - 1.86 (m, 2H), 1.48 - 1.32 (m, 4H), 1.26 - 1.08 (m, 3H), 0.95 - 0.84 (m, 3H) (2 exchangeable protons not observed)	1.29 A 562.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
168		4'-((6-butyl-5-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.01 (d, J=7.9 Hz, 2H), 7.79 (br. s., 1H), 7.57 (d, J=7.9 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.49 - 7.44 (m, 2H), 7.42 (d, J=7.6 Hz, 1H), 7.34 (br. s., 1H), 6.80 (d, J=7.6 Hz, 1H), 6.77 - 6.72 (m, 1H), 6.67 - 6.60 (m, 1H), 6.35 (d, J=7.9 Hz, 1H), 4.37 - 4.06 (m, 2H), 3.68 (d, J=9.8 Hz, 1H), 3.40 - 3.15 (m, 1H), 2.45 - 2.24 (m, 2H), 1.91 (s, 2H), 1.42 - 1.25 (m, 2H), 1.21 - 1.12 (m, 2H), 0.73 (t, J=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.18 A 574.2	A
169		6-butyl-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.52 (s, 1H), 8.46 (d, J=4.3 Hz, 1H), 8.01 (d, J=7.9 Hz, 2H), 7.50 (d, J=7.6 Hz, 2H), 7.26 (d, J=4.3 Hz, 1H), 6.95 (d, J=7.0 Hz, 1H), 6.78 (t, J=7.2 Hz, 1H), 6.64 - 6.56 (m, 1H), 6.40 (d, J=7.9 Hz, 1H), 3.44 - 3.15 (m, 2H), 2.84 - 2.64 (m, 2H), 2.26 (s, 5H), 2.15 (d, J=8.9 Hz, 2H), 1.72 - 1.56 (m, 2H), 1.30 (br. s., 2H), 1.17 - 1.06 (m, 2H), 0.70 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.06 A 544.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
170		3-((2-butyl-4,6-dihydroxy-5-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.67 - 8.55 (m, 1H), 8.14 (d, J=8.2 Hz, 2H), 7.71 (d, J=8.2 Hz, 2H), 7.43 (br. s., 1H), 7.35 (t, J=7.9 Hz, 1H), 7.28 - 7.13 (m, 1H), 7.09 (d, J=7.3 Hz, 1H), 7.05 (d, J=5.8 Hz, 1H), 6.92 (d, J=7.6 Hz, 1H), 3.49 (br. s., 2H), 2.29 (s, 5H), 1.41 (d, J=17.1 Hz, 2H), 1.20 - 1.10 (m, 5H), 0.71 (t, J=7.3 Hz, 3H) (2 exchangeable protons not observed)	0.98 A 543.3	A
171		4'-((6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.01 (d, J=7.9 Hz, 2H), 7.59 - 7.47 (m, 5H), 7.37 (d, J=7.3 Hz, 1H), 7.07 - 6.95 (m, 2H), 6.89 (br. s., 1H), 6.76 (br. s., 1H), 3.56 - 3.46 (m, 2H), 3.11 (s, 3H), 2.92 - 2.70 (m, 6H), 2.32 (br. s., 2H), 1.13 (d, J=5.5 Hz, 2H), 0.70 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.18 A 578.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
172		3-((2-butyl-5-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 (br. s., 1H), 8.01 - 7.90 (m, 2H), 7.48 (br. s., 2H), 7.22 (br. s., 2H), 6.89 (d, J=6.4 Hz, 1H), 6.79 - 6.64 (m, 2H), 3.50 (d, J=9.2 Hz, 2H), 2.27 - 2.05 (m, 5H), 1.37 (br. s., 2H), 1.15 (d, J=7.0 Hz, 2H), 1.02 (br. s., 3H), 0.71 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.21 A 561.3	A
173		6-butyl-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.50 (br. s., 1H), 8.11 (d, J=7.9 Hz, 2H), 7.70 - 7.60 (m, 3H), 7.39 - 7.32 (m, 1H), 7.06 (d, J=7.0 Hz, 1H), 6.93 (d, J=6.4 Hz, 1H), 6.73 (t, J=7.0 Hz, 1H), 6.47 (d, J=7.9 Hz, 1H), 3.49 (br. s., 2H), 3.43 - 3.22 (m, 2H), 2.92 - 2.73 (m, 2H), 2.44 (br. s., 3H), 2.27 (d, J=7.3 Hz, 2H), 1.94 - 1.74 (m, 2H), 1.70 - 1.47 (m, 2H), 1.45 - 1.28 (m, 2H), 0.69 (t, J=6.6 Hz, 3H) (2 exchangeable protons not observed)	1.09 A 544.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
174		4'-((6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.00 (d, J=7.9 Hz, 2H), 7.83 (br. s., 1H), 7.60 (d, J=7.7 Hz, 2H), 7.55 - 7.36 (m, 5H), 7.09 - 6.98 (m, 2H), 6.89 (br. s., 1H), 6.76 (br. s., 1H), 3.12 (br. s., 3H), 2.44 - 2.26 (m, 2H), 1.42 (br. s., 2H), 1.15 (br. s., 2H), 0.72 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.14 A 550.3	A
175		3-((2-butyl-4,6-dihydroxy-5-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.45 (br. s., 1H), 7.92 (d, J=8.2 Hz, 2H), 7.60 (d, J=7.3 Hz, 1H), 7.43 (d, J=7.9 Hz, 2H), 7.34 - 7.29 (m, 1H), 7.21 (t, J=7.8 Hz, 1H), 6.89 (d, J=7.3 Hz, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.66 (br. s., 1H), 3.44 - 3.29 (m, 2H), 2.39 (s, 3H), 2.25 - 2.05 (m, 2H), 1.36 (br. s., 2H), 1.18 - 1.10 (m, 2H), 1.02 (t, J=7.0 Hz, 3H), 0.71 (t, J=7.2 Hz, 3H) (2 exchangeable protons were not observed)	0.96 A 543.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
176		4'-((6-butyl-5-((2-fluorophenyl)(methyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 (d, J=4.6 Hz, 1H), 7.98 - 7.83 (m, 2H), 7.50 (d, J=6.4 Hz, 1H), 7.42 (br. s., 5H), 7.00 - 6.83 (m, 2H), 6.62 (d, J=7.0 Hz, 2H), 3.03 (br. s., 3H), 2.58 (d, J=4.6 Hz, 3H), 2.25 - 2.17 (m, 2H), 1.38 (br. s., 2H), 1.18 - 1.09 (m, 2H), 0.73 (t, J=7.2 Hz, 3H) (2 exchangeable protons were not observed)	1.14 A 564.3	A
177		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.14 (d, J=7.7 Hz, 2H), 7.89 (d, J=8.0 Hz, 1H), 7.67 (d, J=7.2 Hz, 2H), 7.17 - 7.06 (m, 2H), 6.98 (br. s., 1H), 6.77 (br. s., 1H), 6.50 (d, J=7.4 Hz, 1H), 3.46 (br. s., 2H), 2.76 (br. s., 2H), 2.39 (br. s., 3H), 2.29 (d, J=7.3 Hz, 2H), 1.97 - 1.74 (m, 2H), 1.72 - 1.48 (m, 2H), 1.47 - 1.30 (m, 2H), 1.13 (br. s., 2H), 0.69 (br. s., 3H) (2 exchangeable protons were not observed)	1.29 A 562.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
178		3-((2-butyl-5-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-4,6-dihydroxypyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.06 (d, J=8.0 Hz, 2H), 7.87 (t, J=8.1 Hz, 1H), 7.61 (d, J=7.7 Hz, 2H), 7.30 (t, J=7.9 Hz, 1H), 7.12 (d, J=8.0 Hz, 1H), 7.03 (d, J=7.4 Hz, 1H), 6.95 (br. s., 1H), 6.87 (d, J=8.3 Hz, 1H), 3.52 - 3.39 (m, 2H), 2.38 (s, 3H), 2.33 - 2.19 (m, 2H), 1.40 (d, J=6.1 Hz, 2H), 1.20 - 1.08 (m, 5H), 0.72 (t, J=7.3 Hz, 3H) (2 exchangeable protons were not observed)	1.20 A 561.3	A
179		4'-((6-butyl-2,4-dihydroxy-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 (d, J=8.1 Hz, 2H), 7.66 - 7.50 (m, 5H), 7.39 (d, J=7.2 Hz, 1H), 7.10 (d, J=7.4 Hz, 1H), 6.99 (t, J=7.6 Hz, 1H), 6.84 - 6.73 (m, 1H), 6.51 (d, J=8.0 Hz, 1H), 3.31 (d, J=12.6 Hz, 2H), 2.89 (s, 4H), 2.51 - 2.50 (m, 6H), 2.34 - 1.90 (m, 2H), 1.78 (br. s., 2H), 1.49 - 1.28 (m, 2H), 1.13 (br. s., 2H), 0.69 (t, J=6.7 Hz, 3H) (2 exchangeable protons not observed)	1.26 A 600.4	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
180		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.16 (d, J=7.5 Hz, 2H), 7.67 (d, J=7.2 Hz, 2H), 7.30 (d, J=4.3 Hz, 2H), 7.07 (d, J=6.8 Hz, 1H), 6.95 (br. s., 1H), 6.74 (br. s., 1H), 6.49 (d, J=7.7 Hz, 1H), 3.51 (br. s., 2H), 2.28 (br. s., 2H), 2.16 (s, 3H), 1.91 (br. s., 2H), 1.84 - 1.61 (m, 2H), 1.49 - 1.28 (m, 2H), 1.25 - 1.05 (m, 4H), 0.69 (t, J=6.6 Hz, 3H) (2 exchangeable protons not observed)	1.30 A 562.3	A
181		4'-((6-butyl-5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500 MHz, DMSO-d6) δ 8.18 - 7.86 (m, 2H), 7.82 - 7.66 (m, 1H), 7.63 - 7.19 (m, 7H), 7.04 - 6.63 (m, 2H), 2.29 - 2.09 (m, 2H), 1.44 - 1.31 (m, 2H), 1.25 - 1.07 (m, 5H), 1.06 - 0.95 (m, 2H), 0.71 (br t, J=7.2 Hz, 3H) (4 exchangeable protons not observed)	1.53 A 571.2	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
182		4'-((6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.22 (br. s., 1H), 7.97 (d, J=7.7 Hz, 2H), 7.53 (d, J=7.1 Hz, 3H), 7.48 - 7.40 (m, 3H), 6.28 (br. s., 1H), 6.15 (br. s., 2H), 2.59 (d, J=4.4 Hz, 3H), 2.35 - 2.22 (m, 2H), 2.17 - 2.10 (m, 6H), 1.47 - 1.37 (m, 2H), 1.23 (s, 2H), 1.20 - 1.13 (m, 2H), 1.10 (t, J=6.9 Hz, 3H), 0.73 (t, J=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.18 A 588.3	A
183		6-butyl-5-((3,5-dimethylphenyl)(ethyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.49 (br. s., 1H), 8.06 (d, J=7.6 Hz, 2H), 7.72 - 7.56 (m, 3H), 7.35 (br. s., 1H), 6.30 (br. s., 1H), 6.15 (br. s., 2H), 3.65 - 3.58 (m, 1H), 3.52 - 3.36 (m, 1H), 2.43 (br. s., 3H), 2.38 - 2.21 (m, 2H), 2.14 (br. s., 6H), 1.41 (d, J=7.3 Hz, 2H), 1.22 - 1.06 (m, 5H), 0.73 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	0.97 A 546.3	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
184		4'-((6-butyl-2,4-dihydroxy-5-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.09 (br. s., 2H), 7.96 (d, J=7.6 Hz, 2H), 7.56 - 7.49 (m, 1H), 7.47 - 7.37 (m, 4H), 6.98 (d, J=7.0 Hz, 1H), 6.86 - 6.77 (m, 1H), 6.64 (t, J=7.0 Hz, 1H), 6.37 (d, J=7.9 Hz, 1H), 3.25 (d, J=12.5 Hz, 2H), 2.87 - 2.65 (m, 2H), 2.58 (d, J=4.0 Hz, 3H), 2.36 - 2.13 (m, 2H), 2.04 - 1.84 (m, 2H), 1.75 - 1.54 (m, 2H), 1.41 - 1.24 (m, 2H), 1.11 (br. s., 2H), 0.67 (t, J=6.6 Hz, 3H) (2 exchangeable protons not observed)	1.26 A 586.3	B
185		4'-((6-butyl-5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.06 (d, J=4.6 Hz, 1H), 7.87 (d, J=7.9 Hz, 2H), 7.49 (d, J=7.6 Hz, 1H), 7.45 - 7.35 (m, 5H), 7.23 (t, J=7.9 Hz, 1H), 6.90 (d, J=7.3 Hz, 1H), 6.76 (d, J=8.9 Hz, 1H), 6.66 (br. s., 1H), 3.46 - 3.27 (m, 2H), 2.50 - 2.50 (m, 3H), 2.27 - 2.04 (m, 2H), 1.34 (d, J=6.7 Hz, 2H), 1.16 - 1.08 (m, 2H), 1.02 (t, J=7.0 Hz, 3H), 0.68 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.14 A 585.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
186		4'-((6-butyl-5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxypyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.04 (d, J=7.6 Hz, 2H), 7.61 - 7.48 (m, 5H), 7.40 - 7.30 (m, 2H), 7.07 (d, J=6.4 Hz, 1H), 6.99 (br. s., 1H), 6.89 (d, J=7.0 Hz, 1H), 3.61 - 3.48 (m, 2H), 2.51 (br. s., 6H), 2.42 - 2.21 (m, 2H), 1.46 - 1.31 (m, 2H), 1.17 - 1.09 (m, 5H), 0.70 (t, J=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.16 A 599.4	A
187		5-(ethyl(phenyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(2-methylthiazol-5-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.75 - 8.58 (m, 2H), 8.18 (d, J=8.2 Hz, 2H), 7.79 (s, 1H), 7.75 (d, J=7.9 Hz, 2H), 7.55 (d, J=4.6 Hz, 1H), 7.22 - 7.15 (m, 2H), 6.79 - 6.64 (m, 3H), 3.56 (br. s., 2H), 2.67 (s, 3H), 2.32 (s, 3H), 1.05 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.00 A 559.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
188		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(2-methylthiazol-5-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.60 (d, J=4.3 Hz, 1H), 8.18 (s, 1H), 8.13 (d, J=8.2 Hz, 2H), 7.98 (d, J=7.9 Hz, 2H), 7.90 (t, J=6.7 Hz, 2H), 7.78 (s, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.8 Hz, 2H), 6.74 - 6.64 (m, 3H), 3.48 (br. s., 2H), 2.89 (s, 3H), 2.82 (d, J=4.3 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.15 A 601.4	A
189		N-cyclopropyl-4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(2-methylthiazol-5-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.01 (d, J=3.7 Hz, 1H), 7.86 (d, J=7.9 Hz, 1H), 7.75 (s, 1H), 7.59 (s, 1H), 7.38 - 7.32 (m, 3H), 7.31 - 7.21 (m, 3H), 6.98 (t, J=7.6 Hz, 2H), 6.55 - 6.45 (m, 3H), 3.34 - 3.32 (m, 2H), 2.70 (s, 3H), 2.42 - 2.37 (m, 1H), 0.85 (t, J=7.0 Hz, 3H), 0.30 (d, J=7.3 Hz, 2H), 0.00 (br. s., 2H) (2 exchangeable protons not observed)	1.18 A 627.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
190		5-(ethyl(phenyl)amino)-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-6-(2-methylthiazol-5-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.11 (d, J=7.9 Hz, 2H), 7.89 (t, J=8.1 Hz, 1H), 7.77 (s, 1H), 7.66 (d, J=7.6 Hz, 2H), 7.17 (t, J=7.6 Hz, 2H), 7.12 (d, J=6.1 Hz, 1H), 6.73 - 6.65 (m, 3H), 3.57 - 3.47 (m, 2H), 2.67 (s, 3H), 2.39 (s, 3H), 1.03 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.24 A 577.3	A
191		5-(ethyl(phenyl)amino)-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-6-(2-methylthiazol-5-yl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.12 (d, J=4.9 Hz, 1H), 8.03 (d, J=7.9 Hz, 2H), 7.63 (s, 1H), 7.54 (d, J=7.9 Hz, 2H), 7.25 (d, J=4.9 Hz, 1H), 7.08 (t, J=7.6 Hz, 2H), 6.59 (d, J=8.2 Hz, 3H), 3.43 (br. s., 2H), 2.90 (s, 3H), 2.15 (s, 3H), 0.96 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.24 A 577.3	A
192		4'-((5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(2-methylthiazol-5-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.20 (d, J=4.6 Hz, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.79 (s, 1H), 7.61 - 7.52 (m, 3H), 7.50 - 7.40 (m, 3H), 7.24 - 7.12 (m, 2H), 6.75 - 6.64 (m, 3H), 3.53 (br. s., 2H), 2.66 (s, 3H), 2.60 (d, J=4.6 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.14 A 601.3	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
193		6-butyl-3-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-5-(methyl(o-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.17 - 8.05 (m, 2H), 7.63 (d, J=7.0 Hz, 2H), 7.25 (br. s., 1H), 7.12 (br. s., 2H), 6.63 (br. s., 1H), 6.53 (d, J=7.0 Hz, 2H), 3.74 (br. s., 3H), 2.39 - 2.21 (m, 2H), 2.14 (br. s., 3H), 1.38 (br. s., 2H), 1.19 - 1.07 (m, 5H), 0.70 (t, J=7.3 Hz, 3H) (2 exchangeable protons not observed)	1.29 A 536.3	A
194		6-butyl-5-(methyl(o-tolyl)amino)-3-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 - 7.86 (m, 2H), 7.68 - 7.55 (m, 1H), 7.42 (br. s., 2H), 7.32 (br. s., 1H), 7.01 (br. s., 2H), 6.54 - 6.34 (m, 3H), 3.67 (br. s., 3H), 2.55 (s, 3H), 2.17 (br. s., 2H), 1.38 (br. s., 2H), 1.18 - 0.97 (m, 5H), 0.72 (t, J=7.0 Hz, 3H) (2 exchangeable protons not observed)	1.06 A 518.4	B

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
195		4'-((6-butyl-2,4-dihydroxy-5-(methyl(o-tolyl)amino)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.95 (d, J=7.6 Hz, 2H), 7.78 (br. s., 1H), 7.57 - 7.43 (m, 5H), 7.39 (d, J=7.0 Hz, 1H), 7.31 (br. s., 1H), 7.09 (br. s., 2H), 6.58 (br. s., 1H), 6.50 (d, J=7.3 Hz, 2H), 3.68 (br. s., 3H), 2.36 - 2.13 (m, 2H), 1.47 - 1.32 (m, 2H), 1.23 - 1.04 (m, 4H), 0.71 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.19 A 546.4	A
196		4'-((6-butyl-2,4-dihydroxy-5-(methyl(o-tolyl)amino)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.61 - 7.49 (m, 6H), 7.37 (d, J=7.4 Hz, 1H), 7.20 - 7.12 (m, 2H), 6.67 (br. s., 1H), 6.56 (d, J=7.7 Hz, 2H), 3.64 - 3.61 (m, 3H), 2.77 (s, 3H), 2.51 (br. s., 6H), 2.40 - 2.21 (m, 2H), 1.38 (br. s., 2H), 1.14 (d, J=5.9 Hz, 5H), 0.70 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.22 A 574.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
198		6-butyl-3-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-5-(methyl(o-tolyl)amino)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.07 (br. s., 1H), 7.88 (t, J=8.1 Hz, 1H), 7.65 (d, J=7.6 Hz, 2H), 7.20 - 7.06 (m, 3H), 6.71 - 6.63 (m, 1H), 6.57 (d, J=7.9 Hz, 2H), 2.55 (s, 3H), 2.42 - 2.24 (m, 5H), 1.42 (br. s., 2H), 1.21 - 1.09 (m, 5H), 0.72 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.29 A 536.3	B
203		6-butyl-5-(methyl(o-tolyl)amino)-3-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridine-2,4-diol	^{1}H NMR (500MHz, DMSO-d6) δ 8.52 (br. s., 1H), 8.46 (br. s., 1H), 8.04 (br. s., 1H), 7.56 (d, J=7.3 Hz, 2H), 7.27 (d, J=4.0 Hz, 1H), 7.08 (t, J=7.3 Hz, 2H), 6.58 (t, J=6.6 Hz, 1H), 6.50 (d, J=7.9 Hz, 2H), 2.51 (br. s., 6H), 2.24 (s, 3H), 1.45 - 1.35 (m, 2H), 1.21 - 1.13 (m, 2H), 1.09 (t, J=6.9 Hz, 2H), 0.72 (t, J=7.2 Hz, 3H) (2 exchangeable protons not observed)	1.07 A 518.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
206		4'-((6-butyl-2,4-dihydroxy-5-(methyl(o-tolyl)amino)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.94 (d, J=7.9 Hz, 2H), 7.58 - 7.36 (m, 5H), 7.08 (t, J=7.5 Hz, 2H), 6.58 (br. s., 1H), 6.50 (d, J=7.9 Hz, 2H), 3.56 (d, J=10.4 Hz, 3H), 2.58 (d, J=4.6 Hz, 3H), 2.30 - 2.08 (m, 2H), 1.44 - 1.34 (m, 2H), 1.21 - 1.06 (m, 5H), 0.71 (t, J=7.3 Hz, 3H) (3 exchangeable protons not observed)	1.22 A 560.4	A
208		4'-((6-butyl-2,4-dihydroxy-5-(methyl(o-tolyl)amino)pyridin-3-yl)sulfonyl)-N-cyclopropyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.78 (d, J=7.9 Hz, 2H), 7.36 - 7.20 (m, 5H), 6.91 (t, J=7.5 Hz, 2H), 6.41 (t, J=6.7 Hz, 1H), 6.33 (d, J=7.9 Hz, 2H), 2.39 (d, J=3.7 Hz, 1H), 2.31 - 2.28 (m, 3H), 2.15 - 1.97 (m, 2H), 1.27 - 1.15 (m, 2H), 1.02 - 0.87 (m, 5H), 0.52 (t, J=7.2 Hz, 3H), 0.30 (d, J=7.3 Hz, 2H), 0.00 (br. s., 2H) (3 exchangeable protons not observed)	1.21 A 586.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
210		4'-((5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N,N-dimethyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 7.87 (br. s., 2H), 7.64 (br. s., 1H), 7.51 (d, J=7.0 Hz, 1H), 7.46 (br. s., 2H), 7.39 (d, J=6.7 Hz, 2H), 7.33 (d, J=7.0 Hz, 1H), 7.22 (br. s., 1H), 6.92 (d, J=6.4 Hz, 1H), 6.76 (br. s., 2H), 6.15 (br. s., 1H), 3.84 (br. s., 2H), 3.60 (br. s., 3H), 2.72 (br. s., 3H), 2.39 (br. s., 3H), 0.91 (br. s., 3H) (2 exchangeable protons not observed)	1.12 A 623.4	A
211		3-(ethyl(5-((4-(2-fluoro-3-methylpyridin-4-yl)phenyl)sulfonyl)-4,6-dihydroxy-2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 (d, J=4.7 Hz, 1H), 7.99 (d, J=7.2 Hz, 2H), 7.68 (br. s., 1H), 7.51 (d, J=6.7 Hz, 2H), 7.23 (br. s., 2H), 6.95 (d, J=6.9 Hz, 1H), 6.80 (br. s., 1H), 6.18 (br. s., 1H), 3.85 (s, 2H), 3.59 - 3.55 (m, 3H), 2.12 (br. s., 3H), 0.92 (br. s., 3H) (2 exchangeable protons not observed)	1.13 A 585.3	A

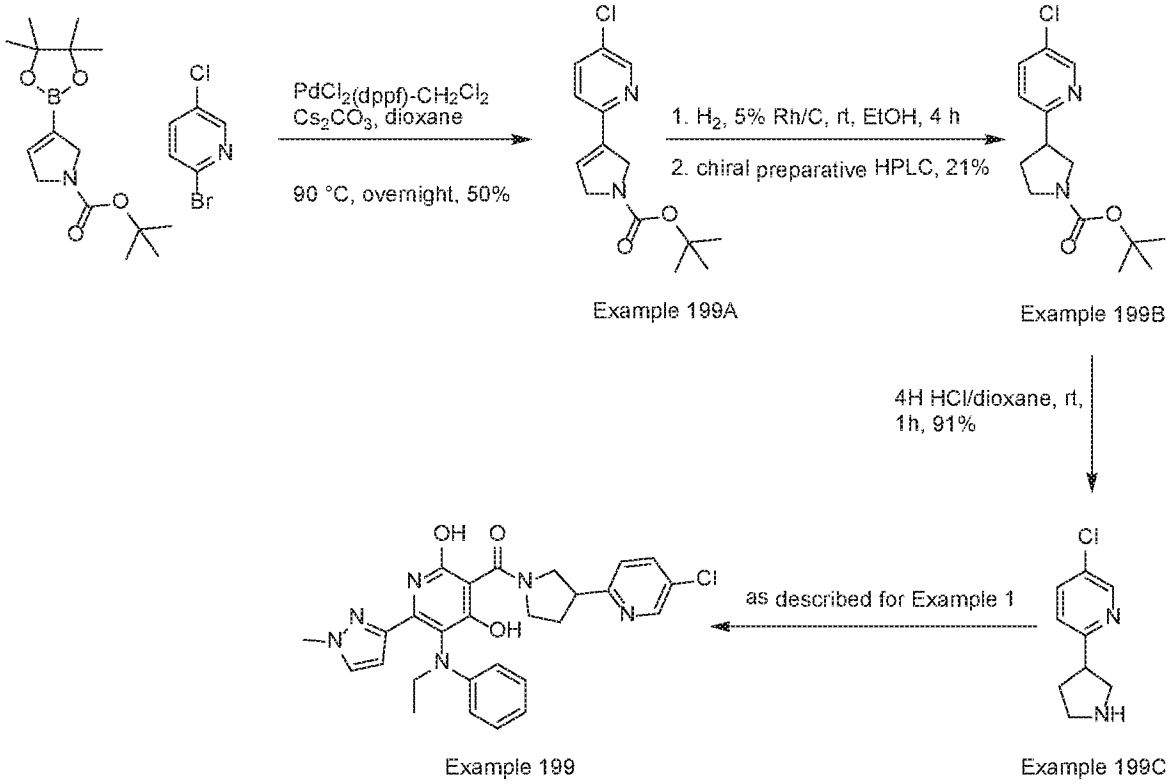
Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
212		3-((4,6-dihydroxy-2-(1-methyl-1H-pyrazol-3-yl)-5-((4-(3-methylpyridin-4-yl)phenyl)sulfonyl)pyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.72 - 8.53 (m, 2H), 8.16 (d, J=8.0 Hz, 2H), 7.79 - 7.67 (m, 3H), 7.41 (br. s., 1H), 7.34 (t, J=8.0 Hz, 1H), 7.28 - 7.15 (m, 1H), 7.13 - 7.04 (m, 3H), 6.96 (d, J=7.9 Hz, 1H), 6.28 (s, 1H), 3.87 (s, 3H), 3.58 (br. s., 2H), 2.28 (s, 3H), 1.02 (t, J=6.9 Hz, 3H) (2 exchangeable protons not observed).	0.89 A 567.4	A
213		3-(ethyl(5-((4-(6-fluoro-2-methylpyridin-3-yl)phenyl)sulfonyl)-4,6-dihydroxy-2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.10 (d, J=6.8 Hz, 2H), 7.87 (br. s., 1H), 7.74 (br. s., 1H), 7.63 (br. s., 2H), 7.31 (br. s., 1H), 7.16 - 7.01 (m, 3H), 6.93 (br. s., 1H), 6.27 (br. s., 1H), 3.87 (br. s., 2H), 3.52 (br. s., 3H), 2.38 (br. s., 3H), 1.01 (br. s., 3H) (2 exchangeable protons not observed)	1.10 A 585.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
214		4'-((5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-methyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.14 (br. s., 1H), 7.88 (d, J=7.9 Hz, 2H), 7.67 (s, 1H), 7.54 - 7.48 (m, 1H), 7.45 - 7.36 (m, 5H), 7.24 (t, J=7.9 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 6.86 - 6.76 (m, 2H), 6.18 (s, 1H), 3.86 (s, 2H), 3.53 (d, J=2.8 Hz, 3H), 2.57 (d, J=4.5 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H) (3 exchangeable protons were not observed)	1.05 A 608.4	A
215		4'-((5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-3-fluoro-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.00 (br. s., 1H), 7.89 (d, J=7.7 Hz, 2H), 7.67 (br. s., 1H), 7.59 (br. s., 1H), 7.54 - 7.46 (m, 3H), 7.29 (t, J=8.8 Hz, 1H), 7.25 - 7.20 (m, 2H), 6.95 (d, J=7.3 Hz, 1H), 6.87 - 6.75 (m, 2H), 6.17 (s, 1H), 3.86 (s, 3H), 3.47 - 3.45 (m, 2H), 0.94 (t, J=6.9 Hz, 3H) (2 exchangeable protons not observed)	1.00 A 613.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
216		4'-((5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.01 (d, J=7.5 Hz, 2H), 7.83 (br. s., 1H), 7.76 - 7.65 (m, 1H), 7.58 (d, J=6.7 Hz, 2H), 7.54 - 7.43 (m, 4H), 7.43 - 7.24 (m, 3H), 7.08 - 6.84 (m, 2H), 6.25 (br. s., 1H), 3.87 (br. s., 2H), 3.66 - 3.60 (m, 3H), 1.00 (br. s., 3H) (2 exchangeable protons not observed)	1.05 A 595.4	A
217		3-((4,6-dihydroxy-2-(1-methyl-1H-pyrazol-3-yl)-5-((4-(2-methylpyridin-3-yl)phenyl)sulfonyl)pyridin-3-yl)(ethyl)amino)benzonitrile	^{1}H NMR (500MHz, DMSO-d6) δ 8.47 (d, J=4.4 Hz, 1H), 7.99 (d, J=7.5 Hz, 2H), 7.68 (br. s., 1H), 7.63 (d, J=6.7 Hz, 1H), 7.51 (d, J=7.2 Hz, 2H), 7.37 - 7.30 (m, 1H), 7.29 - 7.21 (m, 1H), 6.97 (d, J=7.1 Hz, 1H), 6.85 (br. s., 2H), 6.19 (s, 1H), 3.85 (br. s., 2H), 3.73 - 3.70 (m, 3H), 2.40 (br. s., 3H), 0.94 (br. s., 3H) (2 exchangeable protons not observed)	0.87 A 567.4	A

Ex #	Structure	Name	^{1}H NMR	LC/MS RT (min) Method M+H	hAPJ cAMP EC_{50} Potency range
218		4'-((5-((3-cyanophenyl)(ethyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)sulfonyl)-N-cyclopropyl-[1,1'-biphenyl]-2-carboxamide	^{1}H NMR (500MHz, DMSO-d6) δ 8.05 (br. s., 1H), 7.87 (d, J=8.3 Hz, 2H), 7.54 (br. s., 1H), 7.40 - 7.32 (m, 3H), 7.30 - 7.22 (m, 3H), 7.15 (t, J=8.1 Hz, 1H), 6.91 (d, J=6.7 Hz, 2H), 6.76 (d, J=8.3 Hz, 1H), 6.09 (s, 1H), 3.67 (s, 3H), 3.43 - 3.38 (m, 2H), 1.00 - 0.89 (m, 1H), 0.83 (t, J=7.2 Hz, 3H), 0.31 (d, J=6.0 Hz, 2H), 0.00 (br. s., 2H) (2 exchangeable protons not observed)	1.06 A 635.4	A

Example 199. (3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone



Example 199A. ***tert*-butyl 3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate**

A mixture of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (106 mg, 0.360 mmol), 2-bromo-5-chloropyridine (76 mg, 0.40 mmol), cesium carbonate (350 mg, 1.10 mmol) and $PdCl_2(dppf)-CH_2Cl_2$ (18 mg, 0.022 mmol) in dioxane (2.4 mL) and water (0.5 mL) was degassed and heated at 90°C for 14 h. The mixture was diluted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-100% EtOAc/hexane to give **Example 199A** (50 mg, 0.18 mmol, 50 % yield) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.62 - 8.41 (m, 1H), 7.82 - 7.57 (m, 1H), 7.40 - 7.16 (m, 1H), 6.60 - 6.32 (m, 1H), 4.60 - 4.49 (m, 2H), 4.41 - 4.27 (m, 2H), 1.52 - 1.45 (m, 9H).

Example 199B. ***tert*-butyl 3-(5-chloropyridin-2-yl)pyrrolidine-1-carboxylate**

A mixture of **Example 199A** (530 mg, 1.90 mmol) and 5% Rh/C (390 mg, 0.190 mmol) in EtOH (8 mL) was stirred under hydrogen atmosphere (ballon) for 4 h. The mixture was

filtered through Celite and concentrated under reduced pressure. The residue was purified using silica gel chromatography eluting with 0-100% EtOAc/hexane, followed by chiral SFC preparative HPLC (column: Chiralpak IC, 30 x 250 mm, 5 micron; mobile phase: 10 % IPA/0.1%DEA/90% CO_2; flow condition: 85 mL/min, 150 bar, 40 °C; wavelength: 220 nm) to give **Example 199B** (designated as isomer 1, 110 mg, 21% yield). Peak 1 retention time = 11.87 (Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/0.1%DEA/90% CO_2; flow condition: 2.0 mL/min, 150 bar, 40 °C; wavelength: 220 nm. LCMS (Method B) Rt = 0.96 min, *m/z* = 283.2 (M+H). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.52 (d, J=2.2 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.14 (d, J=8.4 Hz, 1H), 3.97 - 3.29 (m, 5H), 2.34 - 2.05 (m, 2H), 1.50 - 1.44 (m, 9H).

Example 199C. ***tert*-butyl 3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate**

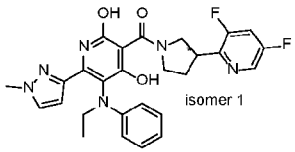
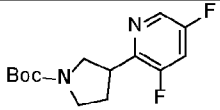
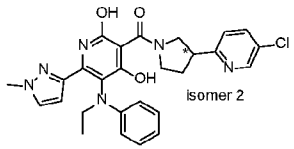
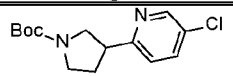
Example 199B (110 mg, 0.38 mmol) and 4N HCl/dioxane (1.0 mL, 4.0 mmol) were stirred at rt for 5 h. The mixture was diluted with diethyl ether, and the solid was collected by filtration to give **Example 199C** (89 mg, 0.348 mmol, 91 % yield) as a white solid. LCMS (Method B) Rt = 0.47 min, *m/z* = 183.1 (M+H). ^{1}H NMR (500MHz, DMSO-d6) δ 7.79 (d, J=2.5 Hz, 1H), 7.24 - 6.97 (m, 1H), 6.83 - 6.56 (m, 1H), 3.01 (s, 1H), 2.83 (s, 2H), 2.77 - 2.67 (m, 1H), 2.54 (br. s., 2H), 1.85 - 1.57 (m, 1H), 1.53 - 1.14 (m, 1H).

Example 199. (6-butyl-5-(2,6-dimethoxyphenyl)-2,4-dihydroxypyridin-3-yl)(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)methanone

Example 199 was prepared from **Example 199C** using the method described for **Example 1**. LCMS (Method A) Rt = 1.13 min, *m/z* = 519.3 (M+H). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (br. s., 1H), 7.86 (br. s., 1H), 7.68 (br. s., 1H), 7.44 (br. s., 1H), 7.12 (d, *J*=6.7 Hz, 2H), 6.60 (d, *J*=8.2 Hz, 3H), 6.23 (br. s., 1H), 3.96 - 3.81 (m, 4H), 3.46 (br. s., 3H), 3.18 (br. s., 1H), 2.35 - 2.01 (m, 4H), 1.07 - 0.93 (m, 3H) (2 exchangeable protons not observed). Human APJ cAMP EC_{50} Potency range A.

The compounds listed in the table below were synthesized using methods analogous to Example 199.

Table 2

Ex #	Structure	Chiral Amine	Name	^{1}H NMR	LC/MS Rt (min) Method M+H	hAPJ cAMP EC_{50} Potency range
197	 isomer 1	 Rt = 4.80, (isomer 1) Whelko (4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 40 °C; wavelength: 220 nm.	(3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.45 (br. s., 2H), 7.87 (br. s., 1H), 7.69 (br. s., 1H), 7.14 (br. s., 2H), 6.73 - 6.52 (m, 3H), 6.20 (br. s., 1H), 3.86 (br. s., 5H), 3.67 - 3.57 (m, 2H), 3.53 - 3.31 (m, 2H), 3.26 (br. s., 1H), 2.31 - 2.03 (m, 2H), 0.98 (br. s., 3H) (2 exchangeable protons not observed)	1.15 A 521.4	A
200	 Isomer 2	 Rt = 2.84, (isomer 2) Whelko (4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 40 °C; wavelength: 220 nm.	(3-(5-chloropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (br. s., 1H), 7.86 (br. s., 1H), 7.68 (br. s., 1H), 7.44 (br. s., 1H), 7.12 (d, *J*=6.7 Hz, 2H), 6.60 (d, *J*=8.2 Hz, 3H), 6.23 (br. s., 1H), 3.96 - 3.81 (m, 4H), 3.46 (br. s., 3H), 3.18 (br. s., 1H), 2.35 - 2.01 (m, 4H), 1.07 - 0.93 (m, 3H) (2 exchangeable protons not observed)	1.14 A 519.4	A

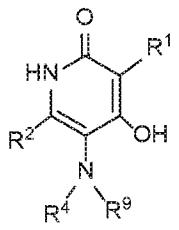
Ex #	Structure	Chiral Amine	Name	^{1}H NMR	LC/MS Rt (min) Method M+H	hAPJ cAMP EC_{50} Potency range
201	isomer 2	Rt = 2.78 (isomer 2) Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 45 °C; wavelength: 220 nm	(3-(2,4-difluorophenyl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.69 (br. s., 1H), 7.47 (d, *J*=7.0 Hz, 1H), 7.25 - 7.01 (m, 4H), 6.69 - 6.56 (m, 3H), 6.22 (br. s., 1H), 3.87 (br. s., 7H), 2.54 (s, 3H), 2.31 - 1.97 (m, 2H), 1.03 - 0.94 (m, 3H) (2 exchangeable protons not observed)	1.19 A 520.4	A
202	isomer 1	Rt = 10.65 (isomer 1) Chiralpak IF, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/90% CO_2; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm	(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)(3-(2-fluorophenyl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.70 (br. s., 1H), 7.45 - 7.26 (m, 2H), 7.22 - 7.10 (m, 4H), 6.69 - 6.56 (m, 3H), 6.23 (br. s., 1H), 4.00 - 3.11 (m, 7H), 2.55 (s, 3H), 2.33 - 1.93 (m, 2H), 1.07 - 0.92 (m, 3H) (2 exchangeable protons not observed)	1.19 A 502.4	A

Ex #	Structure	Chiral Amine	Name	^{1}H NMR	LC/MS Rt (min) Method M+H	hAPJ cAMP EC_{50} Potency range
204		Rt = 8.20 (isomer 2) Whelko (4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 40 °C; wavelength: 220 nm.	(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 8.45 (br. s., 1H), 8.00 (d, *J*=9.8 Hz, 1H), 7.67 (s, 1H), 7.12 (d, *J*=6.7 Hz, 2H), 6.69 - 6.53 (m, 3H), 6.21 (br. s., 1H), 3.86 (s, 3H), 3.71 - 3.55 (m, 3H), 3.54 - 3.34 (m, 2H), 2.49 - 2.46 (m, 2H), 2.26 (br. s., 2H), 0.98 (br. s., 3H) (2 exchangeable protons not observed)	1.24 A 537.0	A
205		Rt = 10.65 (isomer 2) Chiralpak IF, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/90% CO_2; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm	(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)(3-(2-fluorophenyl)pyrrolidin-1-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.70 (br. s., 1H), 7.45 - 7.26 (m, 2H), 7.22 - 7.10 (m, 4H), 6.69 - 6.56 (m, 3H), 6.23 (br. s., 1H), 4.00 - 3.11 (m, 7H), 2.55 (s, 3H), 2.33 - 1.93 (m, 2H), 1.07 - 0.92 (m, 3H) (2 exchangeable protons not observed)	1.17 A 502.4	A

Ex #	Structure	Chiral Amine	Name	^{1}H NMR	LC/MS Rt (min) Method M+H	hAPJ cAMP EC_{50} Potency range
207	isomer 1	Rt = 2.53 (isomer 1) Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 45 °C; wavelength: 220 nm	(3-(2,4-difluorophenyl)pyrrolidin-1-yl)(5-(ethyl(phenyl)amino)-2,4-dihydroxy-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	^{1}H NMR (500MHz, DMSO-d_6) δ 7.69 (br. s., 1H), 7.47 (d, *J*=7.0 Hz, 1H), 7.25 - 7.01 (m, 4H), 6.69 - 6.56 (m, 3H), 6.22 (br. s., 1H), 3.87 (br. s., 7H), 2.54 (s, 3H), 2.31 - 1.97 (m, 2H), 1.03 - 0.94 (m, 3H) (2 exchangeable protons not observed)	1.20 A 520.4	A
209	isomer 2	Rt = 2.78 (isomer 2) Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO_2; flow condition: 3.0 mL/min, 140 bar, 45 °C; wavelength: 220 nm	(3-(2,4-difluorophenyl)pyrrolidin-1-yl)(2,4-dihydroxy-5-(isopropyl(phenyl)amino)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methanone	1H NMR (500 MHz, DMSO-d6) Shift 7.85 (br s, 1H), 7.62 (br s, 1H), 7.50 - 7.28 (m, 2H), 7.18 (br d, J=7.3 Hz, 1H), 7.02 (br s, 2H), 6.61 - 6.46 (m, 2H), 6.18 (br s, 1H), 4.59 - 4.38 (m, 1H), 3.49 (br d, J=10.1 Hz, 6H), 3.22 - 3.14 (m, 1H), 2.89 (s, 3H), 2.23 - 2.12 (m, 2H), 2.05 - 1.90 (m, 4H) (2 exchangeable protons not observed	1.40 A 534.2	A

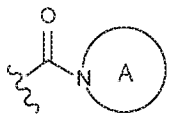
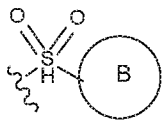
WHAT IS CLAIMED IS:

1. A compound of Formula (I):

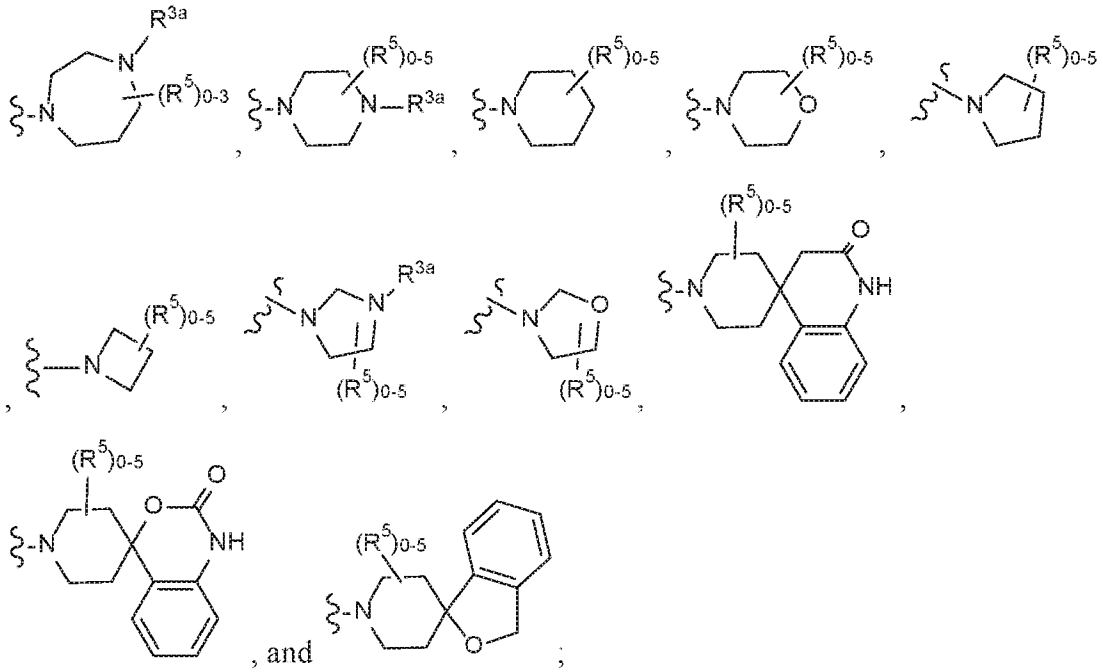


(I)

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

R^1 is independently selected from  and  ;

Ring A is independently selected from



, and ;

Ring B is independently selected from 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;

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, $-(CH_2)_nOR^b$, $-(CH_2)_nNR^aR^a$, $-(CH_2)_nCN$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nC(=O)NR^aR^a$, $-(CH_2)_nNHC(=O)R^b$, $-(CH_2)_nNHC(=O)NR^aR^a$, $-(CH_2)_nNHC(=O)OR^b$, $-(CH_2)_nNHS(O)_pNR^aR^a$, $-(CH_2)_nNHS(O)_pR^c$ $-(CH_2)_nS(O)_pR_c$, $-(CH_2)_nS(O)_pNR^aR^a$, $-(CH_2)_nOC(=O)NR^aR^a$;

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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, aryl, bicyclic carbocyclyl, 6-membered heteroaryl, bicyclic heterocyclyl, each substituted with 1-6 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a mono or bicyclic heterocyclic ring substituted with 1-6 R^{10};

R^{10} 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^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 $-(CH_2)_nNR^fR^f$;

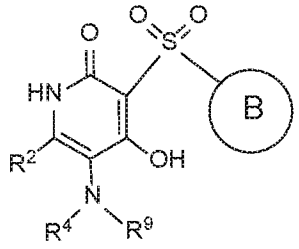
R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl, or R^f and R^f together with the nitrogen

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.

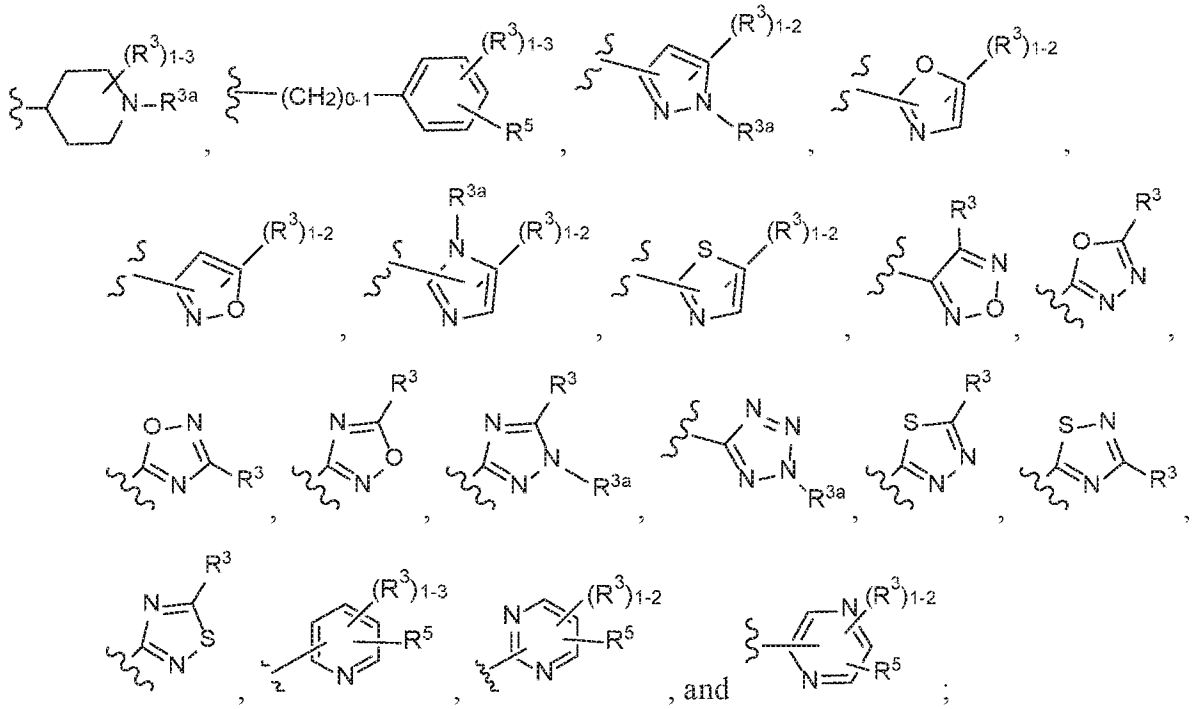
2. The compound of claim 1, having Formula (II):



(II)

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

Ring B is independently selected from



, and ;

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

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 and C_{1-5} alkyl 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 $-NR^aS(O)_pR^6$;

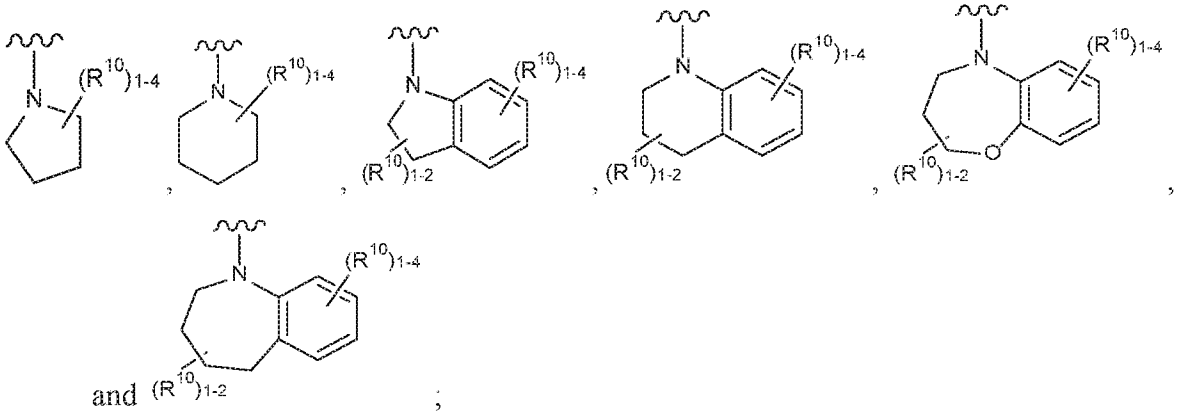
R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

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

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_nOR^b$, $-(CH_2)_nC(=O)R^b$, $-(CH_2)_nC(=O)OR^b$, $-(CH_2)_nNR^aR^a$, 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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, and aryl, each substituted with 1-6 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



and ;

R^{10} 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^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;

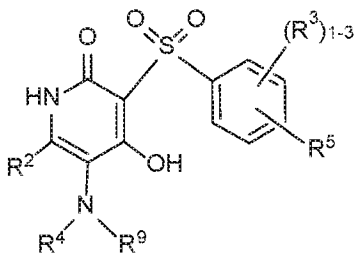
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$,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

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



(III)

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

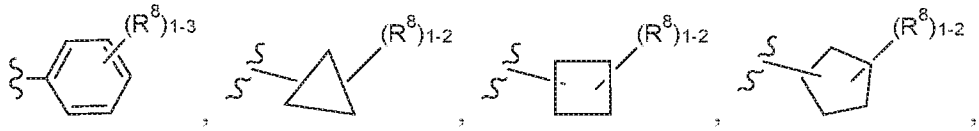
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

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

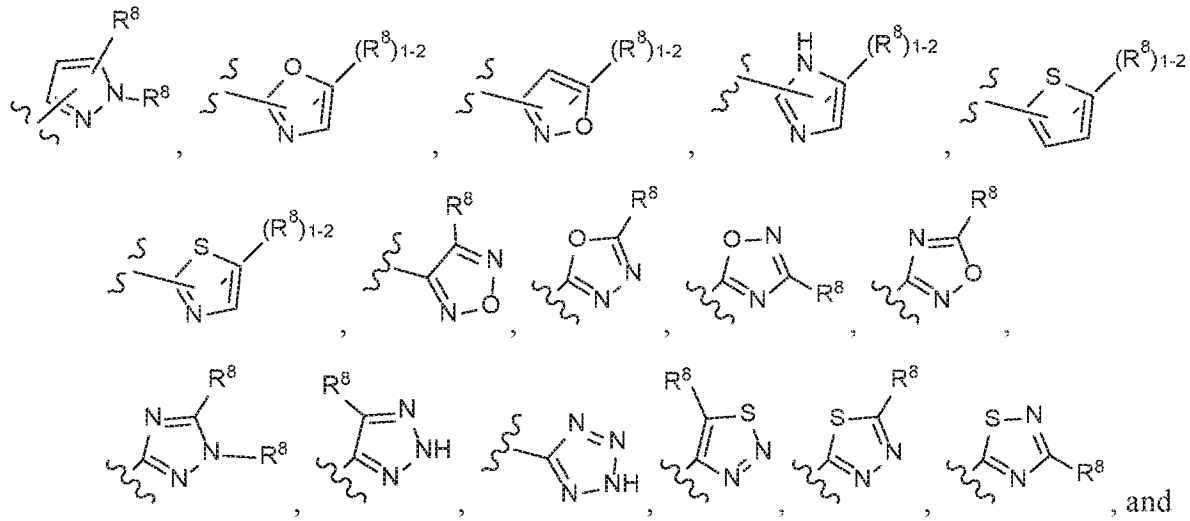
R^4 is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

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

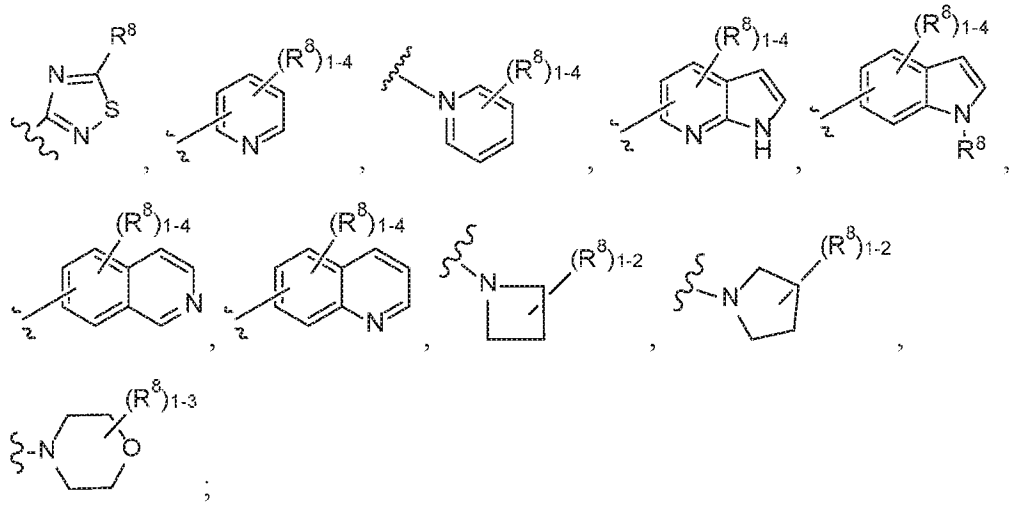
R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from



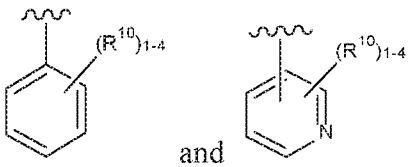
, and



;

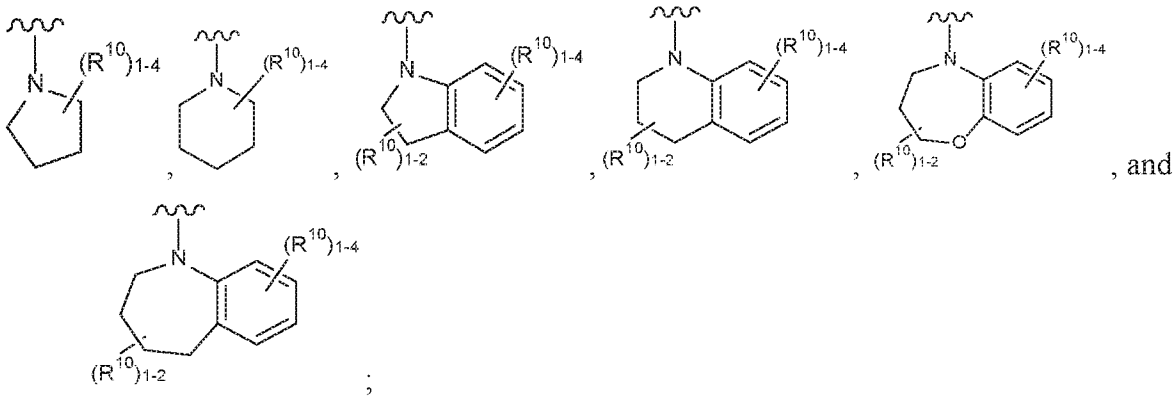
R^8 is independently selected from H, F, Cl, Br, -$(CH_2)_nOR^b$, -$C(=O)R^b$, -$C(=O)OR^b$, -NR^aR^a, CN, -$C(=O)NR^aR^a$, -$NHC(=O)OR^b$, C_{1-4} alkyl substituted with 0-3 R^e, -$(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^9 is independently selected from



and ;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



, and

;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

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;

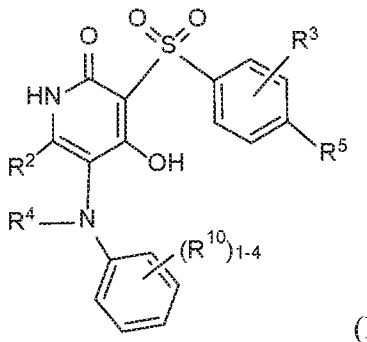
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n-C_{4-6}$ heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$,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

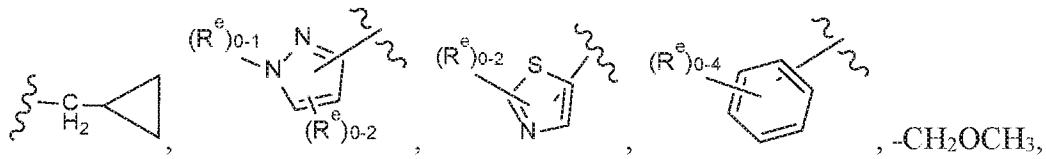
4. The compound of claim 3, having formula (IV):



(IV)

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

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

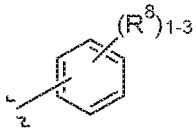
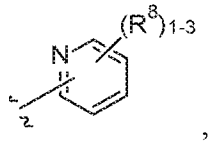
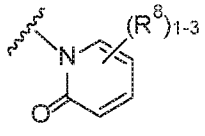
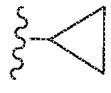


, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OCH(CH_3)_2$;

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

R^4 is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH_2(CH_3)_2$;

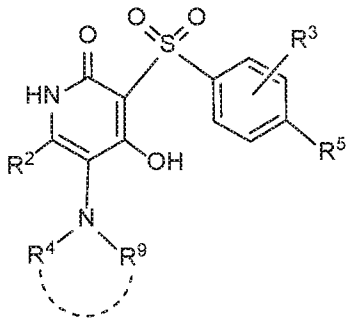
R^5 is R^6;

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

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl and $-C(=O)N(C_{1-4}alkyl)_2$; and

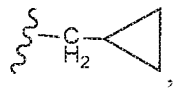
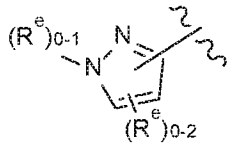
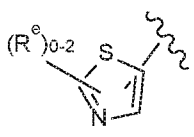
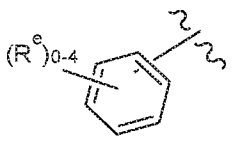
R^{10} is independently selected from H, F, Cl, CN, $-CH_3$, $-CH_2CH_3$, and -OMe.

5. The compound of claim 3, having formula (V):



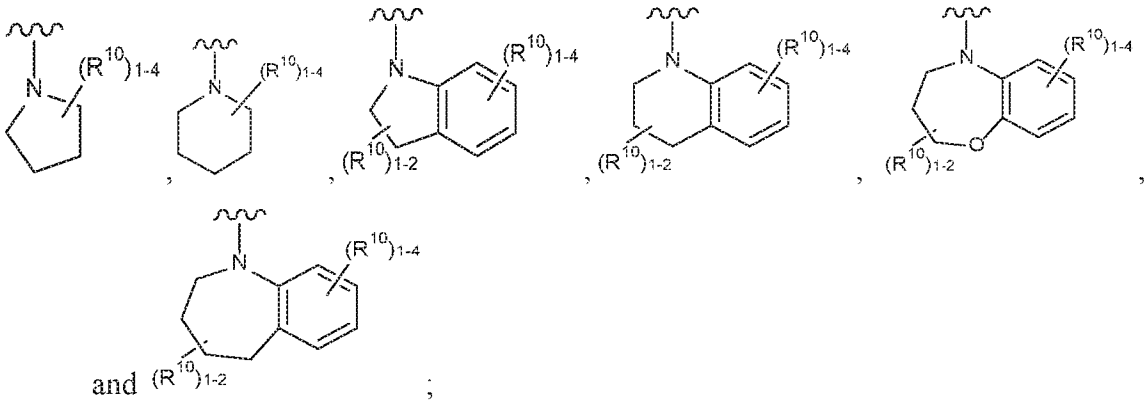
(V)

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

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 $-CH_2OCH(CH_3)_2$;

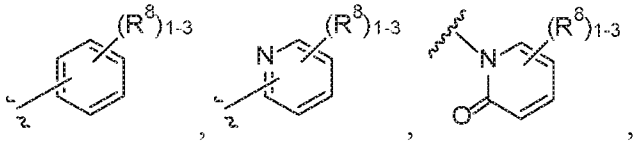
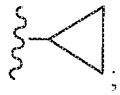
R^3 is independently selected from H, F, Cl, and Br;

R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



and ;

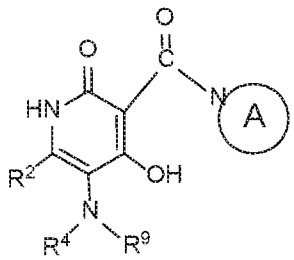
R^5 is R^6;

R^6 is independently selected from  , and  ;

R^8 is independently selected from H, F, Cl, Br, $-(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl and $-C(=O)N(C_{1-4}alkyl)_2$; and

R^{10} is independently selected from H, F, Cl, CN, $-CH_3$, $-CH_2CH_3$, and $-OCH_3$.

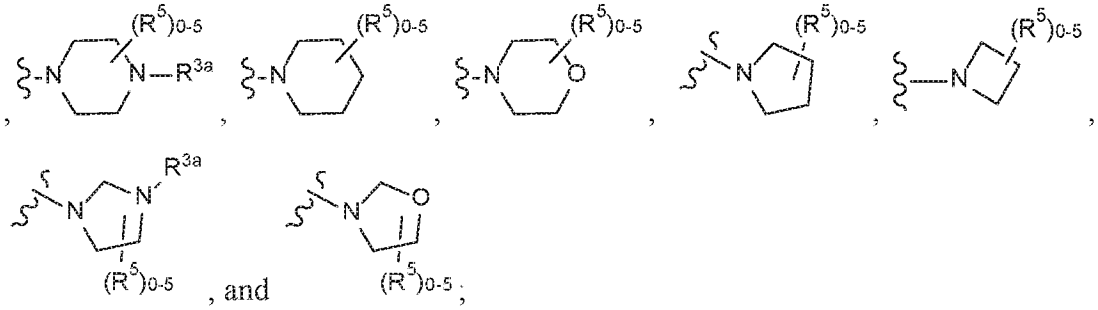
6. The compound of claim 2, having Formula (VI):



(VI)

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

Ring A is independently selected from



, and ;

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^{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 and C_{1-5} alkyl 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 $-NR^aS(O)_pR^6$;

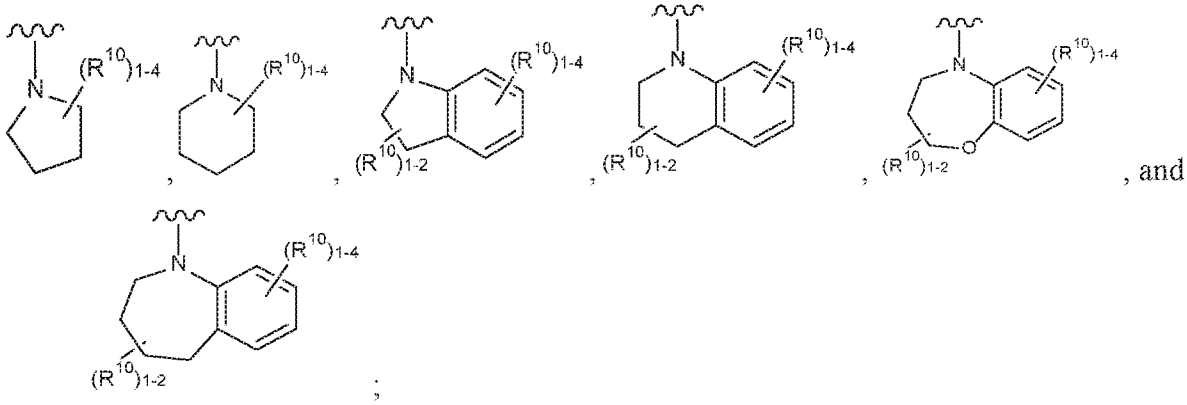
R^6 is independently selected from $-(CR^7R^7)_n$-aryl, $-(CR^7R^7)_n$-C_{3-6} cycloalkyl, and $-(CR^7R^7)_n$-heteroaryl, each substituted with 1-4 R^8;

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^9 is independently selected from C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, and aryl, each substituted with 1-3 R^{10};

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



R^{10} 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^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 $-(CH_2)_nNR^fR^f$;

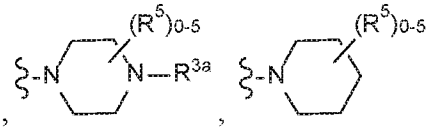
R^f is independently selected from H, F, Cl, Br, CN, OH, C_{1-5}alkyl (optimally substituted with F, Cl, Br and OH), C_{3-6} cycloalkyl, and phenyl;

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

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

7. The compound according to claim 6, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein

Ring A is independently selected from



, and ;

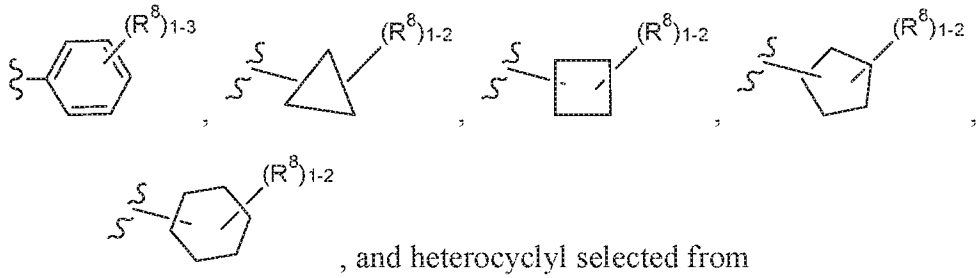
R^2 is independently selected from C_{1-5} alkyl substituted with 0-3 R^e; C_{2-5} alkenyl, aryl substituted with 0-3 R^e, 5-6 membered heterocyclyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, $-(CH_2)_{1-4}OC_{1-5}$alkyl, and $-(CH_2)_{1-3}OC_{3-6}$cycloalkyl;

R^{3a} is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

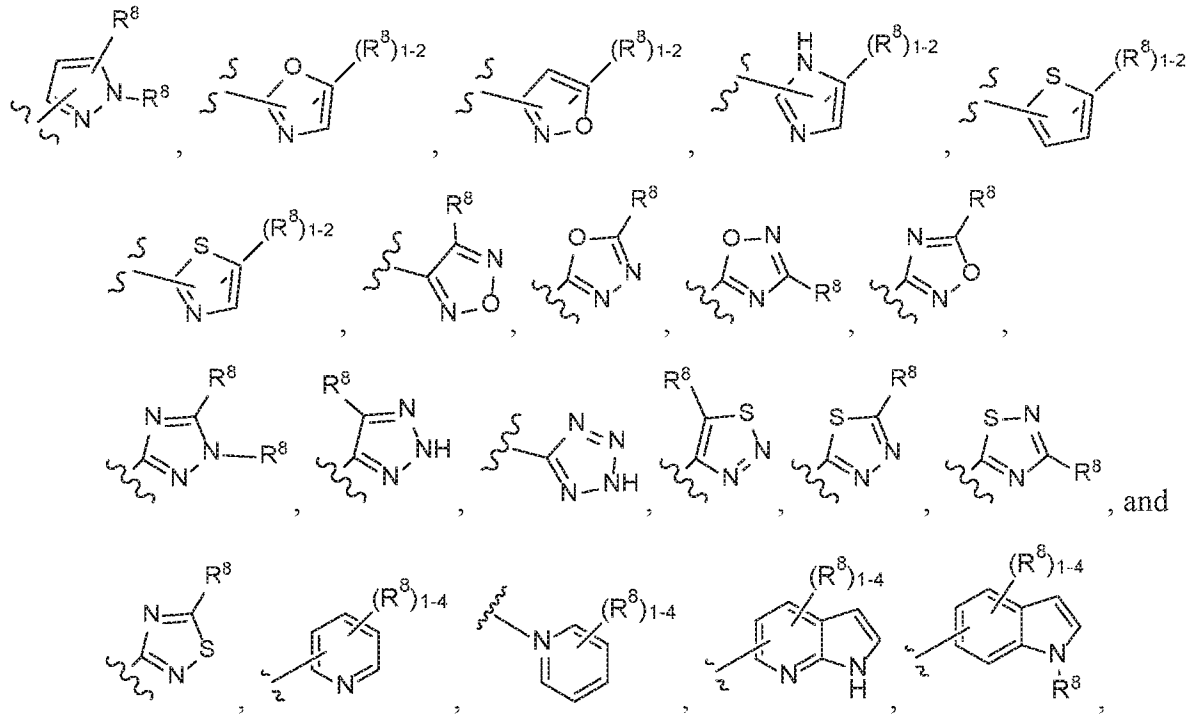
R^4 is independently selected from H and C_{1-5} alkyl substituted with 0-3 R^e;

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

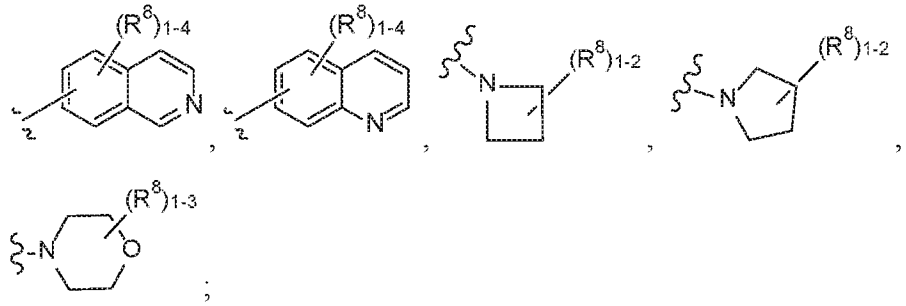
R^6 is independently selected from carbocyclyl selected from



, and heterocyclyl selected from

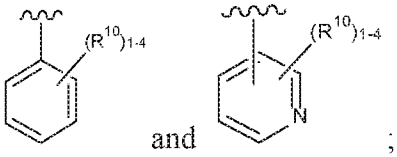


, and



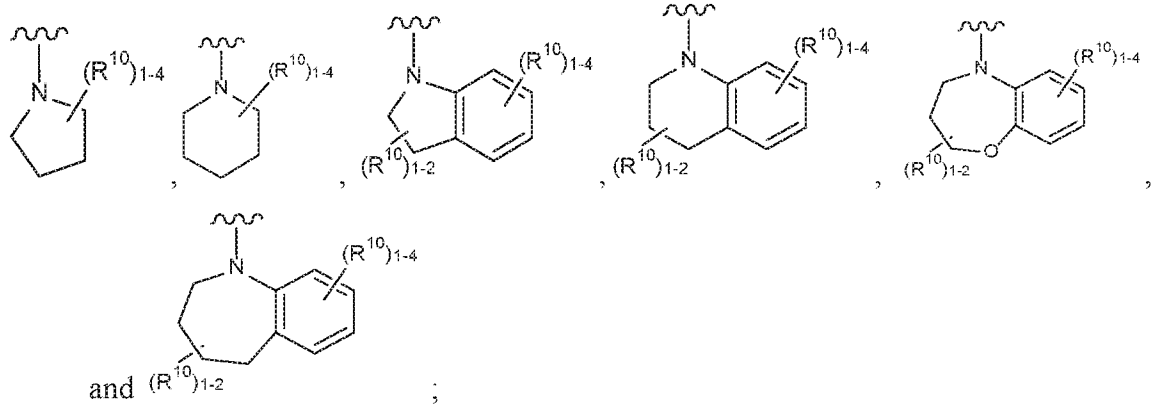
R^8 is independently selected from H, F, Cl, Br, -OR^b, -C(=O)R^b, -C(=O)OR^b, -NR^aR^a, CN, -C(=O)NR^aR^a, -NHC(=O)OR^b, C_{1-4} alkyl substituted with 0-3 R^e, -$(CH_2)_n$-C_{3-6} carbocyclyl substituted with 0-3 R^e, and -$(CH_2)_n$-heterocyclyl substituted with 0-3 R^e;

R^9 is independently selected from



;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

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;

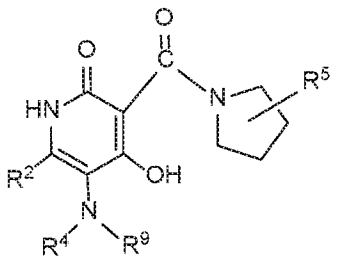
R^e is independently selected from C_{1-6} alkyl substituted with 0-5 R^f, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-C_{4-6} heterocyclyl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, CO_2H, $-(CH_2)_nOR^f$, $S(O)_pR^f$, $C(=O)NR^fR^f$, $NR^fC(=O)R^f$,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

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



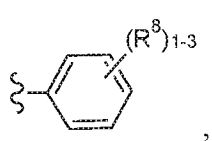
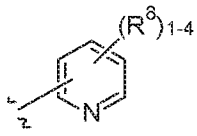
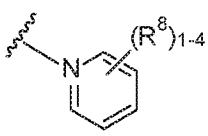
(VII)

or a stereoisomer, an enantiomer, a diastereomer, 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, 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;

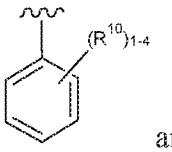
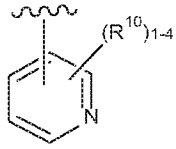
R^4 is independently selected from H and C_{1-4} alkyl;

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

R^6 is independently selected from  ,  , and  ;

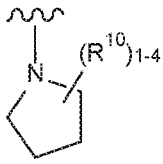
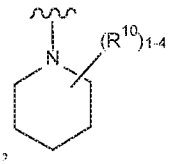
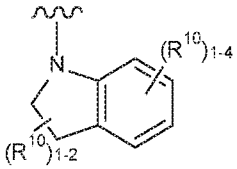
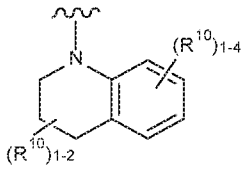
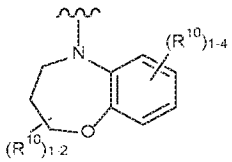
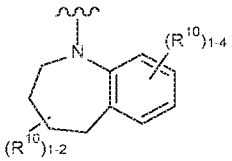
R^8 is independently selected from H, F, Cl, Br, -$(CH_2)_{0-1}OC_{1-4}$ alkyl, C_{1-4} alkyl, and -C(=O)N(C_{1-4}alkyl)$_2$;

R^9 is independently selected from

and ;

alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from






, and

;

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl;

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;

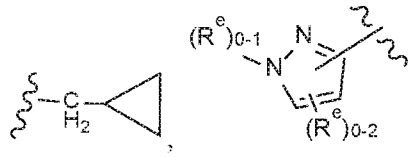
R^b is independently selected from H, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-10}carbocyclyl, and heterocyclyl substituted with 0-5 R^e;

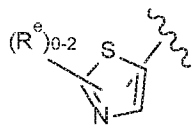
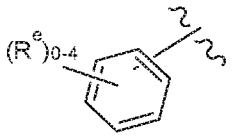
R^e is independently selected from C_{1-6} alkyl (optionally substituted with F and Cl), OH, OCH_3, OCF_3, -$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-C_{4-6} heterocyclyl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, F, Cl, Br, CN, NO_2, =O, and CO_2H; and

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

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

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

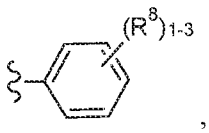
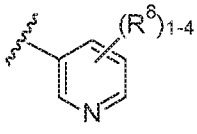
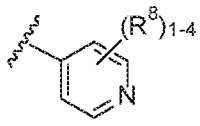
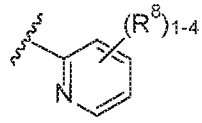


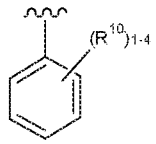
, -CH_2OCH_3, -$CH_2OCH_2CH_3$, and -$CH_2OCH(CH_3)_2$;

R^4 is independently selected from -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, and -$CH_2(CH_3)_2$;

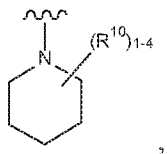
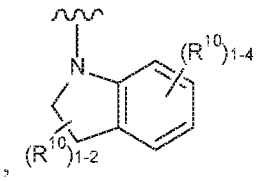
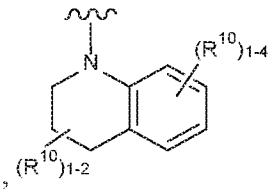
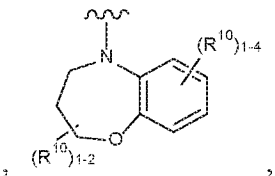
R^5 is R^6;

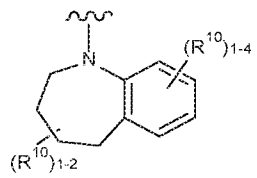
R^6 is independently selected from  ,  ,  , and  ;

R^8 is independently selected from H, F, Cl, and Br;

R^9 is  ;

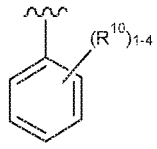
alternatively, R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from

, and  ; and

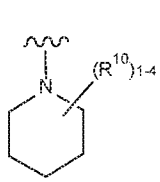
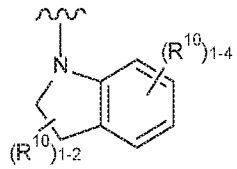
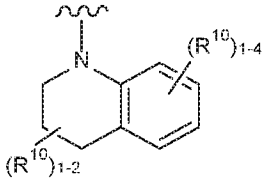
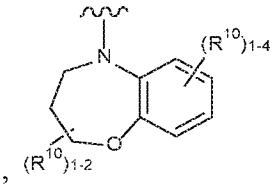
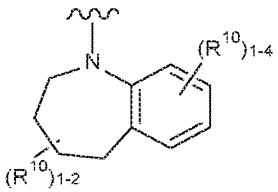
R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

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

R^9 is  ; and

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

11. The compound according to claim 9, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^9 together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from

 ,  ,  ,  , and  ; and

R^{10} is independently selected from H, F, Cl, CN, C_{1-4} alkyl, and OC_{1-4} alkyl.

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/US2017/056265

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 C07D401/06 C07D401/14 C07D413/14 C07D401/04
C07D413/04 C07D417/04 C07D417/14 A61K31/4427 A61P9/00
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, CHEM ABS Data, 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	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 abstract page 152; figure 3 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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
13 December 2017	21/12/2017

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	Stix-Malaun, Elke

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/056265

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/188073 A1 (RES TRIANGLE INST [US]; RUNYON SCOTT P [US]; MAITRA RANGAN [GB]; NARAY) 10 December 2015 (2015-12-10) page 1 examples claims	1-15

A,P	WO 2017/066402 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 20 April 2017 (2017-04-20) abstract examples claims	1-15

A,P	WO 2016/196771 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 8 December 2016 (2016-12-08) examples claims	1-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/056265

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015188073 A1	10-12-2015	AU 2015269247 A1	01-12-2016
		CA 2949559 A1	10-12-2015
		CN 106459004 A	22-02-2017
		EP 3152200 A1	12-04-2017
		JP 2017523126 A	17-08-2017
		KR 20170012305 A	02-02-2017
		PE 06642017 A1	10-06-2017
		US 2016207889 A1	21-07-2016
		WO 2015188073 A1	10-12-2015
WO 2017066402 A1	20-04-2017	TW 201720796 A	16-06-2017
		UY 36949 A	28-04-2017
		WO 2017066402 A1	20-04-2017
WO 2016196771 A1	08-12-2016	AR 104884 A1	23-08-2017
		TW 201708214 A	01-03-2017
		US 2016355507 A1	08-12-2016
		UY 36705 A	30-11-2016
		WO 2016196771 A1	08-12-2016